The JUPITER Trial: How Will It Change Clinical Practice?

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Several studies have shown that baseline levels of high-sensitivity C-reactive protein (hs-CRP) in apparently healthy men and women are predictive of future cardiovascular events. In primary prevention, hs-CRP levels could indicate which primary prevention patients are at higher risk and might benefit from preventive statin therapy. Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) aimed to determine whether treatment with rosuvastatin 20 mg/d would reduce the rate of first major cardiovascular events among apparently healthy individuals with low-density lipoprotein cholesterol (LDL-C) levels below 130 mg/dL, but with hs-CRP levels of 2 mg/L or higher. At the time of study closure, it was found that treatment with rosuvastatin significantly reduced the primary composite endpoint by 44% as compared with placebo. Results of the JUPITER trial clearly suggest that patients with elevated hs-CRP stand to benefit from statin therapy, regardless of their LDL-C level.

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Coronary heart disease (CHD) remains one of the leading causes of death in the world today, and despite promising preventive and treatment strategies, mortality rates from CHD remain unacceptably high.[1] Over the past several decades, strategies for the prevention of CHD have been applied broadly both at the population level and in the individual patient. One of the most effective strategies has been lipid-lowering therapy. Major clinical trials of lipid-lowering therapy in patients both with and without CHD have been conducted over the past decade. Many of the collected data involve the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins).

These trials have established convincingly that lowering of low-density lipoprotein cholesterol (LDL-C) by drugs, in addition to diet, reduces the incidence of fatal and nonfatal myocardial infarction in both primary and secondary prevention.[2]

Although the role of statins in secondary prevention of cardiovascular events and mortality is well established, their value for primary prevention had been less clear. A 2006 analysis in patients without cardiovascular disease concluded that although statin therapy decreased the incidence of major coronary and cerebrovascular events and revascularizations, it did not reduce the risk of CHD events or overall mortality.[3] In addition, the use of statins in primary prevention has been hampered by calculations of "cost-effectiveness" and "numbers needed to treat" to prevent 1 cardiovascular event, which obscured the risk:benefit ratio of statin therapy in primary prevention. Although targeting statin therapy to higher-risk primary prevention patients would be one way to improve cost-effectiveness and lower the number needed to treat, to most efficiently target therapy, better screening methods would be needed in primary prevention. Classically, risk stratification involves use of traditional cardiovascular risk factor assessment or risk models that use traditional risk factors such as those in the Framingham Risk Score. The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines focus risk-reduction strategies on management of dyslipidemia and use the Framingham Risk Score to target patients who require either more or less intensive lipid-lowering therapy. The current risk stratification paradigm, however, is not always robust enough in primary prevention to detect which patients are at high enough risk to make the number needed to treat small enough to ensure that preventive statin therapy will be cost-effective.

In an effort to improve cardiovascular risk stratification, significant attention has focused on high-sensitivity C-reactive protein (hs-CRP). Several studies have shown that baseline levels of hs-CRP in apparently healthy men and women are predictive of future cardiovascular events.[4] This means that, in primary prevention, hs-CRP may have the ability to detect which primary prevention patients are at higher risk and, therefore, may warrant preventive statin therapy.

Rationale for the JUPITER Trial

Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) was a large, multinational, long-term, double-blind, placebo-controlled, randomized clinical trial of statin therapy (rosuvastatin 20 mg/d). The primary objective of the JUPITER trial was to determine whether treatment with rosuvastatin 20 mg/d would reduce the rate of first major cardiovascular events—defined as the combined endpoint of cardiovascular death, stroke, myocardial infarction, hospitalization for unstable angina, or arterial revascularization—among apparently healthy individuals with LDL-C levels below 130 mg/dL, but with hs-CRP levels of 2 mg/L or higher. The JUPITER trial was specifically designed to address the following question: Will statin therapy prevent a first cardiovascular event among individuals with LDL-C levels below 130 mg/dL, but who are presumably at increased vascular risk because of elevated levels of hs-CRP? The authors estimated that within the United States alone, as many as 25 to 30 million adults might fall into this potentially high-risk category.[5]

Design of the JUPITER Trial

The JUPITER trial was funded by the pharmaceutical company AstraZeneca (Wilmington, DE), which makes and markets rosuvastatin. AstraZeneca had no access to unblinded trial data and played no role in analysis or interpretation of the study data or in manuscript preparation. This study randomized 17,802 healthy men and women to rosuvastatin 20 mg/d or placebo.[6] Healthy men ages 50 or older and healthy women ages 60 or older were eligible for the trial if at the initial screening visit they had an LDL-C level of less than 130 mg/dL and an hs-CRP level of 2.0 mg/L or more. Other inclusion criteria 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/dL. 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 3 times the upper limit of the normal range.
- A creatinine level that was higher than 2.0 mg/dL.
- 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 normal).
- A recent history of alcohol or drug abuse or another medical condition that might compromise safety or the successful completion of the study.
- Inflammatory conditions, such as severe arthritis, lupus, or inflammatory bowel disease.
- Use of 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) during that interval. Only subjects who successfully completed the run-in phase were enrolled.

JUPITER was an event-driven trial designed to continue until 520 confirmed primary endpoints were established. The trial's prespecified monitoring plan called for 2 interim efficacy analyses.

Results of the JUPITER Trial

In this trial, 38.5% of subjects were women, and 25% of subjects were African American or Hispanic. The median body mass index was 28.3, and the median blood pressure was 134/80 mm Hg. NCEP ATP III criteria for diagnosis of the metabolic syndrome was met by 41% of participants. Median LDL-C was 108 mg/dL, median high-density lipoprotein cholesterol was 49 mg/dL, and median hs-CRP was 4.3 mg/L (Table 1).

Among patients treated with rosuvastatin, LDL-C levels were reduced from 108 mg/dL at baseline to 55 mg/dL at 12 months. Levels of hs-CRP were reduced from 4.2 mg/L at baseline to 2.2 mg/L at 12 months (Table 2). Triglyceride levels were reduced 17% from baseline among those treated with rosuvastatin.

On March 29, 2008, the first prespecified efficacy evaluation was held, and at that time, the independent data and safety monitoring board recommended termination of the trial because of convincing evidence of a reduction in cardiovascular morbidity and mortality among patients treated with rosuvastatin compared with those treated with placebo. Therefore, the JUPITER trial was prematurely terminated after a mean follow-up of only 1.9 years.

At the time of study closure, it was found that treatment with rosuvastatin significantly reduced the primary composite endpoint by 44% as compared with placebo (Figure 1). This reduction was observed across

Table 1
Patient Characteristics in the JUPITER Trial

	Rosuvastatin (n = 8901)	Placebo (n = 8901)
Age, Years (median)	66 (range, 60-71)	66 (range, 60-71)
Female	3426 (38.5%)	3375 (37.9%)
Ethnicity		
White	6358 (71.4%)	6325 (71.1%)
Black	1100 (12.4%)	1124 (12.6%)
Hispanic	1121 (12.6%)	1140 (12.8%)
Blood Pressure, mm (median)		
Systolic	134 (range, 124-145)	134 (range, 124-145)
Diastolic	80 (range, 75-87)	80 (range, 75-87)
Smoker	1400 (15.7%)	1420 (16.0%)
Family History	997 (11.2%)	1048 (11.8%)
Metabolic Syndrome	3652 (41.0%)	3723 (41.8%)
Aspirin Use	1481 (16.6%)	1477 (16.6%)

JUPITER, Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin. Adapted with permission from Ridker PM et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med.* 2008;359:2195-2207.[6]

Table 2
Levels of LDL-C and hs-CRP During the JUPITER Study

	Baseline	12 mo
LDL-C		
Rosuvastatin 20 mg	108	55
Placebo	108	110
hs-CRP		
Rosuvastatin 20 mg	4.2	2.2
Placebo	4.3	3.5

LDL-C, low-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; JUPITER, Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin. Data from Ridker PM et al.[6]

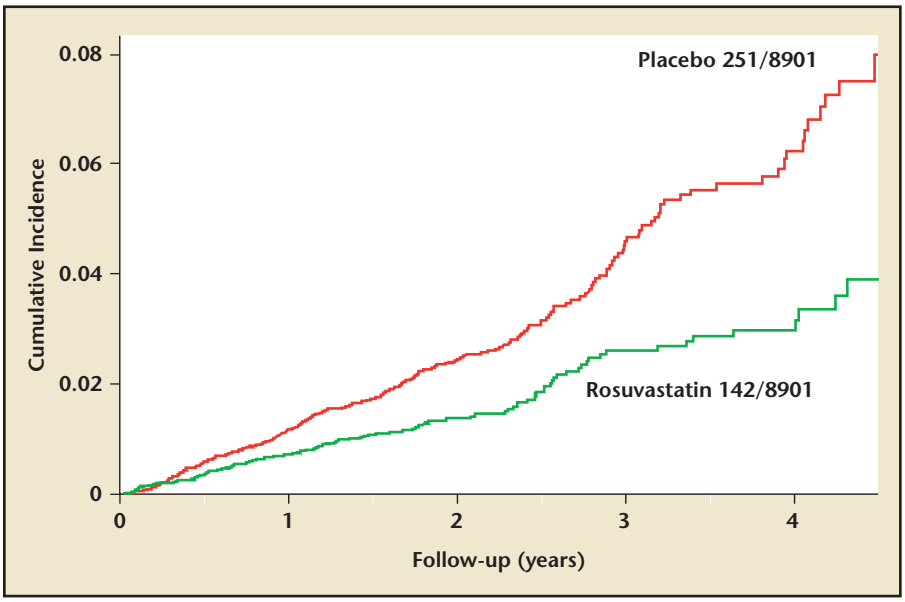

Figure 1. *In the JUPITER trial, treatment with rosuvastatin significantly reduced the primary composite endpoint (cardiovascular death, stroke, myocardial infarction, hospitalization for unstable angina, or arterial revascularization) by 44% as compared with placebo. JUPITER, Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin. Adapted with permission from Ridker PM et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein.* N Engl J Med. *2008;359:2195–2207.*[6]

the range of individual endpoints that comprised the composite. It included a 55% reduction in nonfatal myocardial infarction, a 48% reduction in nonfatal stroke, a 46% reduction in revascularizations, and a 47% reduction in the risk of hard cardiac events (a composite of myocardial infarction, stroke, and death from cardiovascular causes) (Table 3).

In addition, subgroup analysis revealed that for the primary endpoint, there was no evidence of heterogeneity in the results for any subgroup evaluated. Importantly, risk reductions in the rosuvastatin group were similar for women (46%) and men (42%) and for every subgroup evaluated, including the elderly, different racial or ethnic groups, and among all Framingham risk scores.

Side Effects

Most of the monitored side effects were similar in incidence between the rosuvastatin and the placebo groups. Notable exceptions, however, were seen in median glomerular filtration rates at 12 months (66.8 and 66.6 mL per minute per 1.73 m^2 of body-surface area in the rosuvastatin and placebo groups, respectively [P = .02]); median glycated hemoglobin value (5.9% and 5.8%, in the rosuvastatin and placebo groups, respectively [P = .001]); and physician-reported diabetes (270 reports

Table 3
Results From the JUPITER Trial

Endpoint	Rosuvastatin Group (n = 8901), n	Placebo Group (n = 8901), n	Hazard Ratio (95% CI)
Primary endpoint*	142	251	0.56 (0.46-0.69)
Nonfatal MI	22	62	0.35 (0.22-0.58)
Any MI	31	68	0.46 (0.30-0.70)
Nonfatal stroke	30	58	0.52 (0.33-0.80)
Any stroke	33	64	0.52 (0.34-0.79)
Revascularization	71	131	0.54 (0.41-0.72)
Hospitalization for unstable angina	16	27	0.59 (0.32-1.10)
Revascularization or hospitalization for unstable angina	76	143	0.53 (0.40-0.70)
MI, stroke, or death from cardiovascular causes	83	157	0.53 (0.40-0.69)
Total mortality	198	247	0.80 (0.67-0.97)

*Cardiovascular death, stroke, myocardial infarction, hospitalization for unstable angina, or arterial revascularization.
JUPITER, Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin; CI, confidence interval; MI, myocardial infarction.
Adapted with permission from Ridker PM et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med.* 2008;359:2195–2207.[6] Reprinted from Watson KE et al.[10]

vs 216 reports in the rosuvastatin and placebo groups, respectively [P = .01]).

Implications of the JUPITER Trial

If results from the placebo group in the JUPITER trial are extrapolated over 10 years, the 10-year risk of hard CHD events (myocardial infarction and cardiovascular death) would be approximately 6%, and this group could be considered a low-risk population. For such patients, therefore, current guidelines might not recommend LDL-C–lowering therapy, such as a statin.

It is not clear, however, that the JUPITER population was actually low risk and, in fact, JUPITER may have identified a higher risk population due to the high prevalence of overweight/obesity and the metabolic syndrome. More than 40% of participants in JUPITER had the metabolic syndrome, so it is not certain that simply extrapolating the 1.9% event rate out to 10 years will provide an accurate estimate of the 10-year risk of a hard CHD event.

Questions Raised by the JUPITER Trial

Results of the JUPITER trial clearly suggest that patients with elevated hs-CRP stand to benefit from statin therapy, regardless of their LDL-C level. Several questions, however, still do remain to be answered.

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Should all patients receive an hs-CRP test, and should hs-CRP be added to standard risk prediction models? Although the JUPITER trial selected participants with elevated hs-CRP levels, it was not a trial of an hs-CRP–based risk assessment strategy. Such hs-CRP–inclusive risk prediction strategies have been suggested[7,8] and validated retrospectively, but they have not been prospectively tested in clinical trials.

Which patients should receive an hs-CRP test? It is estimated that only about 4% of the US population meets the JUPITER criteria—elevated hs-CRP, but without significant elevation of other markers—and the JUPITER investigators needed to screen nearly 90,000 individuals to enroll the ultimate cohort of 17,802. Thus, widespread hs-CRP screening could potentially occur without an alteration in therapy.

Should hs-CRP levels be followed serially, and, if so, should therapy be altered based on the findings? In the JUPITER trial, hs-CRP was assessed once at entry and was not followed serially. No data support the utility of following hs-CRP levels and using them to alter statin therapy.

What is the target LDL-C goal for patients with elevated hs-CRP? Because the JUPITER participants were treated with either placebo or rosuvastatin 20 mg/d, this trial provides no data on alternate doses of rosuvastatin or on the targeting of specific LDL-C levels.

If hs-CRP falls to within normal levels, should statin therapy be

Main Points

- Although the role of statins in secondary prevention of cardiovascular events and mortality is well established, their value for primary prevention had been less clear.
- One of the most effective strategies for prevention of coronary heart disease has been lipid-lowering therapy.
- Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) was designed to determine whether statin therapy could prevent a first cardiovascular event among individuals with low-density lipoprotein cholesterol (LDL-C) levels below 130 mg/dL, but who are presumably at increased vascular risk because of elevated levels of high-sensitivity C-reactive protein (hs-CRP).
- Among patients treated with rosuvastatin, LDL-C levels were reduced from 108 mg/dL at baseline to 55 mg/dL at 12 months. Levels of hs-CRP were reduced from 4.2 mg/L at baseline to 2.2 mg/L at 12 months. Triglyceride levels were reduced 17% from baseline among those treated with rosuvastatin.
- The JUPITER trial was terminated early because of convincing evidence of a reduction in cardiovascular morbidity and mortality among patients treated with rosuvastatin compared with those treated with placebo.
- At the time of study closure, it was found that treatment with rosuvastatin significantly reduced the primary composite endpoint by 44% as compared with placebo.

continued? Should individuals with elevated hs-CRP also receive other preventive therapies, such as aspirin?

What were the data regarding diabetes? The results indicated that 1 out of every 200 persons treated with rosuvastatin for primary prevention for 1.9 years will develop new-onset diabetes.

Is this effect real? Will it affect longer-term outcomes? Are these results applicable to all statins?

What are the medical-economic implications of the JUPITER trial? Cardiovascular disease remains a leading cause of death throughout the world. Utilization of preventive therapies is critical to reducing the burden of cardiovascular disease. To most effectively and efficiently apply preventive therapies, cardiovascular risk stratification is of paramount importance. Current risk stratification models, although offering many benefits, fail to identify some higher risk patients, and thus additional risk stratification tools are being sought. Measurement of hs-CRP levels is one of the emerging risk stratification tools being used.

Conclusion

Current guidelines recommend measurement of hs-CRP levels in patients at intermediate risk of a CV event based on global risk assessment.[9] In the JUPITER trial, however, individuals considered to be at low risk, but with hs-CRP levels exceeding 2 mg/L, derived significant benefit from rosuvastatin therapy after a mean follow-up of 1.9 years. This trial has the potential to change clinical practice in important and profound ways, yet several clinical questions remain. Addressing these questions will lead to refinements in risk assessment, tailoring of preventive therapies, and, ultimately, it is hoped, to reduction in coronary heart disease. ■

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