

## EDITORIAL



## Expanding the Orbit of Primary Prevention — Moving beyond JUPITER

Mark A. Hlatky, M.D.

The aphorism “prevention is better than cure” makes perfect sense when applied to healthy habits such as following a sensible diet, maintaining an ideal body weight, exercising regularly, and not smoking. But increasingly, prevention of cardiovascular disease includes drug therapy, particularly statins to lower cholesterol levels. Statins were first tested in subjects at high risk for coronary events, and the limits of treatment have subsequently been expanded to include persons at progressively lower risk.<sup>1</sup> The results of the Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER; ClinicalTrials.gov number, NCT00239681), reported by Ridker et al. in this issue of the *Journal*,<sup>2</sup> might push the orbit of statin therapy outward to include even more of the general population. Before pharmacologic treatment for primary prevention is expanded further, however, the evidence should be examined critically.

The JUPITER trial enrolled healthy subjects who did not have high cholesterol levels, according to conventional benchmarks.<sup>3</sup> The entry criterion of a low-density lipoprotein (LDL) cholesterol level of less than 130 mg per deciliter (3.4 mmol per liter) is below the currently recommended threshold for initiating pharmacologic treatment for primary prevention, although treatment at this level is indicated in patients who have clinical coronary disease or diabetes.<sup>3</sup> In JUPITER, a high-sensitivity C-reactive protein level of 2.0 mg per liter or higher was an additional entry criterion to identify higher-risk subjects. The trial of nearly 18,000 patients was stopped, with only 1.9 of its proposed 4 years of follow-up concluded, when the data

and safety monitoring board noted a significant reduction in the primary end point among participants assigned to receive rosuvastatin (142 primary events, vs. 251 in the placebo group; hazard ratio, 0.56; 95% confidence interval [CI], 0.46 to 0.69). There was a similar reduction in a combination of the more important hard outcomes: myocardial infarction, stroke, or death from cardiovascular causes (83 events in the rosuvastatin group vs. 157 in the placebo group; hazard ratio, 0.53; 95% CI, 0.40 to 0.69).

The results of JUPITER raise two important questions about the primary prevention of coronary disease. Should indications for statin treatment be expanded? And how should measurements of high-sensitivity C-reactive protein be used?

The relative risk reductions achieved with the use of statin therapy in JUPITER were clearly significant. However, absolute differences in risk are more clinically important than relative reductions in risk in deciding whether to recommend drug therapy, since the absolute benefits of treatment must be large enough to justify the associated risks and costs. The proportion of participants with hard cardiac events in JUPITER was reduced from 1.8% (157 of 8901 subjects) in the placebo group to 0.9% (83 of the 8901 subjects) in the rosuvastatin group; thus, 120 participants were treated for 1.9 years to prevent one event.

On the other side of the balance, of concern are the significantly higher glycated hemoglobin levels and incidence of diabetes in the rosuvastatin group in JUPITER (3.0%, vs. 2.4% in the placebo group;  $P=0.01$ ). There are also no data on

the long-term safety of lowering LDL cholesterol to the level of 55 mg per deciliter (1.4 mmol per liter), as was attained with rosuvastatin in JUPITER, which is lower than in previously reported trials. Long-term safety is clearly important in considering committing low-risk subjects without clinical disease to 20 years or more of drug treatment. Finally, the cost of rosuvastatin (roughly \$3.45 per day) is much higher than that of generic statins.

The measurement of high-sensitivity C-reactive protein has been shown to improve the estimation of the risk of coronary events.<sup>4</sup> An elevated high-sensitivity C-reactive protein level was an entry criterion for JUPITER, but coronary disease is affected by multiple factors, and high-sensitivity C-reactive protein was just one of several indicators of participants' cardiovascular risk. It is unlikely that high-sensitivity C-reactive protein testing is the only way to identify subjects who will benefit from treatment, since statins have reduced the relative risk to a similar extent for every other indicator of cardiovascular risk.<sup>1</sup> Ridker et al. suggest, from their meta-regression analysis, that the risk reduction observed in JUPITER was greater than that expected on the basis of previous trials. Meta-regression is not a reliable technique, however, and the early termination of JUPITER owing to the efficacy data probably exaggerated the results to some degree.<sup>5</sup>

The design of JUPITER means that the study provides only limited and indirect information about the role of high-sensitivity C-reactive protein testing in clinical management, since the trial did not compare subjects with and those without high-sensitivity C-reactive protein measurements, nor did it compare the use of high-sensitivity C-reactive protein with the use of other markers of cardiovascular risk. It also did not ascertain whether subjects with a high-sensitivity C-reactive protein level of less than 2.0 mg per liter would benefit from treatment.

In evaluating how to use high-sensitivity C-reactive protein testing in practice, it is important to understand how the participants in JUPITER were selected. The 89,890 subjects who attended a clinic visit appear to have been prescreened to exclude those who had previous lipid-lowering therapy, diabetes, elevated serum creatinine levels, or poorly controlled hypertension. At the screening visit, approximately 80% of the re-

maining subjects were excluded, most because of LDL cholesterol or high-sensitivity C-reactive protein levels. To understand who might benefit from high-sensitivity C-reactive protein testing, there should be a detailed analysis of how the estimated (and actual) cardiovascular risk of the screened subjects changed on the basis of their high-sensitivity C-reactive protein levels, particularly in relation to generally accepted risk thresholds and in key subgroups such as women.

At this point, the current guideline for measurement of high-sensitivity C-reactive protein<sup>4</sup> remains reasonable: a measurement may be obtained in asymptomatic individuals who have an intermediate level of risk, as estimated on the basis of standard clinical risk markers, if the decision to initiate drug treatment might change depending on the high-sensitivity C-reactive protein level. In my view, the evidence still favors this selective strategy for measuring high-sensitivity C-reactive protein, not routine measurement.

There is increasing recognition that laboratory and screening tests need to be evaluated according to their effects on clinical management and outcomes, not just risk levels. Randomized trials have shown that performing mammography,<sup>6</sup> screening for abdominal aortic aneurysm,<sup>7</sup> and performing coronary angiography after acute myocardial infarction<sup>8</sup> improve outcomes. However, JUPITER was a trial of statin therapy, not high-sensitivity C-reactive protein testing. A true randomized trial of evaluation and treatment guided by the high-sensitivity C-reactive protein level would provide a direct assessment of the clinical value of such testing.

JUPITER provides yet more evidence about the effectiveness of statin therapy in reducing cardiovascular risk, even among persons who would not currently be considered for pharmacotherapy.<sup>3</sup> Guidelines for primary prevention will surely be reassessed on the basis of the JUPITER results, but the appropriate size of the orbit of statin therapy depends on the balance between the benefits of treatment and its long-term safety and cost.

Dr. Hlatky reports receiving grant support from the American Heart Association Pharmaceutical Roundtable for the Stanford-Kaiser Cardiovascular Outcomes Research Center. No other potential conflict of interest relevant to this article was reported.

This article (10.1056/NEJMe0808320) was published at [www.nejm.org](http://www.nejm.org) on November 9, 2008.

From the Stanford University School of Medicine, Stanford, CA.

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