On February 9, 2010, the US Food and Drug Administration (FDA) extended its approval of rosuvastatin to include the indication for reducing the risk of stroke, myocardial infarction (MI), and revascularization procedures in individuals who have normal low-density lipoprotein cholesterol (LDL-C) levels and no clinically evident coronary heart disease but have an increased risk based on age, high-sensitivity C-reactive protein (hsCRP) levels, and the presence of at least 1 additional cardiovascular disease risk factor. The decision by the FDA was based on results from the Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) study, which demonstrated a 44% risk reduction in the primary end point in 17 802 primary prevention patients randomly allocated to treatment with rosuvastatin, 20 mg, compared with placebo.

Although the results of the JUPITER trial were first presented in November 2008, they continue to invite public controversy, as reflected in 2 recent articles published in the New York Times and Time magazine that appeared to question the overzealous effort to extend statin treatment to a relatively healthy population.

See also page 1032

These partisan reactions have polarized the cardiovascular community into 2 camps—the skeptics and the advocates. The resultant confusion poses a dilemma for practitioners and patients alike. Herein, we critically review the JUPITER trial to provide practical recommendations to the practicing clinician with respect to the following 3 key questions: (1) Should hsCRP be used to stratify treatment decisions as in JUPITER? (2) How reliable is the favorable benefit-risk assessment in JUPITER? And (3) what are the implications for guideline recommendations?
But even if the association was stronger, a purist might yet argue that without a low–LDL-C, low-hsCRP arm, it is not possible to evaluate the utility of hsCRP in JUPITER. The JUPITER investigators justified this exclusion because a post hoc analysis of Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) trial (on which the JUPITER hypothesis was based) showed no treatment benefit among patients with low LDL-C and low hsCRP values. Imagine if women were excluded from the trial, as were subjects with low hsCRP levels, because women are known to be at lower risk than men. Would we then use the results in men to justify withholding treatment in women? If the exclusion of women tells us nothing about gender, then JUPITER tells us nothing about hsCRP.

A prespecified primary efficacy analyses in JUPITER in subgroup of participants by LDL-C and hsCRP levels found that the highest treatment effect (63% risk reduction) was observed in the subgroup with above median baseline LDL-C and below median baseline hsCRP levels (Table 1). However, there was no significant intergroup difference in treatment response. Although these subgroup analyses are deficient in power, they lend no support to the hypothesis of dependence of treatment effect on hsCRP.

Table 1. Treatment Effect According to Baseline Low-Density Lipoprotein Cholesterol and High-Sensitivity C-Reactive Protein Levels in JUPITER.

<table>
<thead>
<tr>
<th>LDL-C</th>
<th>hsCRP</th>
<th>Interaction Termb</th>
<th>Interaction Termb</th>
<th>Interaction Termb</th>
<th>Interaction Termb</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ Median</td>
<td>Median</td>
<td>&gt; Median</td>
<td>≤ Median</td>
<td>Median</td>
<td>&gt; Median</td>
</tr>
<tr>
<td>0.50 (0.30-0.81)</td>
<td>0.74 (0.51-1.07)</td>
<td>0.68 (0.36-1.26)</td>
<td>0.76 (0.37-1.64)</td>
<td>0.68 (0.36-1.26)</td>
<td>0.76 (0.37-1.64)</td>
</tr>
<tr>
<td>0.37 (0.24-0.57)</td>
<td>0.66 (0.44-0.99)</td>
<td>0.56 (0.31-1.01)</td>
<td>0.76 (0.37-1.64)</td>
<td>0.68 (0.36-1.26)</td>
<td>0.76 (0.37-1.64)</td>
</tr>
<tr>
<td>0.74 (0.38-1.43)</td>
<td>0.89 (0.51-1.54)</td>
<td>0.68 (0.36-1.26)</td>
<td>0.76 (0.37-1.64)</td>
<td>0.68 (0.36-1.26)</td>
<td>0.76 (0.37-1.64)</td>
</tr>
</tbody>
</table>

Interaction termb 0.74 (0.38-1.43) 0.66 (0.44-0.99) 0.56 (0.31-1.01) 0.76 (0.37-1.64) 0.68 (0.36-1.26) 0.76 (0.37-1.64)

Abbreviations: hsCRP, high-sensitivity C-reactive protein; JUPITER, Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin; LDL-C, low-density lipoprotein cholesterol; Pint, interaction P value.

SI conversion factors: To convert LDL-C to millimoles per liter, multiply by 0.0259; to convert hsCRP to nanomoles per liter, multiply by 9.524. To convert hsCRP to nanomoles per liter, multiply by 9.524. Compared with placebo, treatment with rosuvastatin significantly reduced cardiovascular events in every hsCRP category. Pint indicates interaction P value.

Figure. Treatment effect by high-sensitivity C-reactive protein (hsCRP) categories. Data are stratified according to 3 different hsCRP cut points: 4.2 mg/L (median), 4.0 mg/L, and 3.0 mg/L (American Heart Association/Center for Disease Control and Prevention cut point for high risk) (to convert hsCRP to nanomoles per liter, multiply by 9.524). Compared with placebo, treatment with rosuvastatin significantly reduced cardiovascular events in every hsCRP category. Pint indicates interaction P value.
tor of risk and treatment response in JUPITER. Nevertheless, some of the analyses of hsCRP on which this judgment is based were post hoc, included only a select subset of the entire spectrum of values (given the restrictive entry criterion for an hsCRP level >2 mg/L), used arbitrary thresholds rather than as a continuous variable, and did not fully explore the potential confounding impact of gender (women have both higher hsCRP levels and lower event rates) on the relationship between baseline hsCRP levels and risk within JUPITER.

**HOW RELIABLE IS THE BENEFIT-RISK ASSESSMENT IN JUPITER?**

JUPITER was an event-driven trial designed to detect a 25% reduction in risk of a major cardiac event. Two interim analyses were prespecified, the first after three-eighths of the projected 520 outcome events occurred, and the second after three-fourths of the outcome events occurred. The second analysis was actually conducted after only five-eighths of the events occurred (328 instead of the planned 390 events). Based on this second analysis, the Independent Data Monitoring Board recommended early termination of the study after a median follow-up of 1.9 years instead of the projected 4 years. The details of the stopping rules on which this decision was based were not published in the primary report. Such decisions are often controversial. On the one hand, critics have argued that stopping the trial prematurely may have introduced biases, potentially resulting in an overestimate of benefit and an underestimate of harm. On the other hand, the JUPITER investigators have defended the decision, offering evidence that argues against any substantive impact the early termination had on the magnitude of treatment effect.

Although it is not possible to directly adjudicate whether the observed treatment benefit in JUPITER was biased by this decision (since we do not know what the true effect is), nevertheless, several indirect lines of evidence point toward the possibility of an exaggerated benefit. First, based on previous meta-analyses, lowering LDL-C by 40 mg/dL (to convert to millimoles per liter, multiply by 0.0259) is expected to reduce ischemic events by 25% after 2 to 3 years and by 30% after 4 years (with a corresponding 10% reduction in mortality). Compared with these projections, the benefit in ischemic events (including mortality) in JUPITER is unexpectedly large and rapid. Second, the observed treatment effect exceeded the expected 25% difference (presumably based on the clinical judgment of the investigators and prior evidence) the study was designed to detect by nearly 2-fold. Third, prematurely truncated trials are notorious for being vulnerable to being truncated trials overestimate benefit.10 A recently published systematic review of 515 trials reported that most truncated trials overestimate benefits compared with their matched completed trials. On average, the ratio of relative risks in the truncated and matching completed trials was 0.71. For example, for treatments that showed 20% benefit in completed trials (relative risk, 0.80), a truncated trial would overestimate the benefit by more than 2-fold on average (relative risk, 0.57). The difference was independent of the presence of statistical stopping rules used by data monitoring committees and was greatest in trials with less than 500 outcome events. As a result, the report urged data monitoring committees to wait until substantial numbers of events have accrued before suggesting an early end to a trial. Given that the perils of stopping trials are not trivial—the risks include a false-positive result, an overoptimistic result, a less-convincing result, or a missed opportunity to gather essential data on adverse effects—we support this statement.

Estimates from a given trial that seem implausibly high can be moderated by using Bayesian methods to incorporate information from earlier trials. According to Goodman, the smaller the treatment effect observed in earlier trials, the greater the likelihood of bias introduced from early stopping, and vice versa. At the time JUPITER was stopped, the Independent Data Monitoring Board had access to data from the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) trial (that assessed rosvastatin therapy in a high-risk population with ischemic heart failure patients), which was published earlier. The results showed a lack of significant improvement in cardiovascular outcomes despite similar lowering of LDL-C (45% vs 47% in JUPITER) and hsCRP (32% vs 38% in JUPITER) levels with rosvastatin in CORONA. A Bayesian integration of CORONA and JUPITER is given in Table 2. The key finding is that the updated estimates are substantially more conservative. The treatment benefit is mod-
erated down from 20% to 8% with respect to mortality, from 47% to 13% with respect to the combined end point of cardiovascular death, MI, or stroke, and from 54% to 27% with respect to MI—estimates that are in alignment with the results of subsequent rosuvastatin trials. The corresponding absolute risk difference in cardiovascular death, MI, or stroke end point is reduced from a 0.83% to 0.23%, and the number needed to treat increased from 119 to 434. This has important implications for clinical practice, cost-effectiveness assessment, and policy and public health discussions.

Thus, the treatment benefit in JUPITER, although real, is likely to be overestimated and the risk is likely to be underestimated.

**WHAT ARE THE IMPLICATIONS FOR GUIDELINES AND CLINICAL PRACTICE?**

The results of the JUPITER trial were recently incorporated into the 2009 Canadian Cardiovascular Society (CCS) Guidelines for the Diagnosis and Treatment of Dyslipidemia and Prevention of Cardiovascular Disease in the Adult. The guideline recommends that men 50 years or older and women 60 years or older who are at moderate risk for cardiovascular disease (10%-20% by the Framingham Risk Score) and whose level of LDL-C level is lower than 135 mg/dL might be candidates for testing for elevated hsCRP level, since such individuals have been shown to benefit from statin treatment if they have an hsCRP level higher than 2.0 mg/L (class IIA, level B). It is important to note that approximately 22% of subjects in JUPITER would have qualified for lipid-lowering therapy even without elevated hsCRP level according to the 2004 National Cholesterol Education Program modifications of the Third Adult Treatment Panel (ATP III) guidelines based on 2 risk factors, a 10-year CHD risk of 10% to 20%, and LDL-C level of 100 to 129 mg/dL at baseline. Moreover, a post hoc analysis by the FDA showed that when the Framingham Risk Score risk categories were stratified according to elevated hsCRP level using the median cut point of 4.2 mg/L, the treatment effect was consistently greater in the below-median compared with the above-median hsCRP subgroup. The intergroup difference achieved statistical significance in the intermediate risk subjects (66% vs 35% risk reduction; Pint = .02). These data appear to challenge the guideline recommendation that higher concentrations of hsCRP might predict preferential benefit from statins, with the caveat that without including subjects with a hsCRP level lower than 2 mg/L, it is not possible to fully evaluate the impact of a wider range of hsCRP level on treatment response.

Although JUPITER showed that the lowest cardiovascular event rate was achieved in subjects who attained the “dual targets” of LDL-C level lower than 70 mg/dL and an hsCRP level lower than 2 mg/L, presently, hsCRP is not recommended by the guidelines as a secondary target of therapy based on the lack of clinical trial evidence that targeting a particular hsCRP level results in clinical benefit.

**CONCLUSIONS**

Based on a critical appraisal of the JUPITER trial, we conclude that the 3 take-home messages for the practicing clinician are the following: (1) do not stratify treatment decisions by hsCRP level (without including both a low and high hsCRP arm, it is not possible to assess if hsCRP has any utility in treatment decisions); (2) do not expect 50% risk reductions in outcomes (early stopping likely contributed to an overexuberant estimate of benefit and perhaps to an underestimate of risk); and (3) do not forget diet, exercise, weight loss, and risk factor control (lifestyle modification trumps pharmacologic intervention for primary prevention, but if patients do not modify their lifestyle, statins can be used judiciously). These recommendations should suffice, at least until the next generation of guideline recommendations reignites the controversy.

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**REFERENCES**


