The JUPITER Trial
Results, Controversies, and Implications for Prevention
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Statin therapy is effective at reducing cardiovascular event rates among those with prior myocardial infarction, stroke, diabetes, or overt hyperlipidemia, and current guidelines strongly recommend lipid-lowering therapy among these patient groups as an adjunct to aggressive lifestyle interventions. However, of the nearly 1.7 million heart attacks and strokes that occur annually in the United States, more than half occur among apparently healthy men and women with average or low levels of cholesterol. Thus, novel screening and treatment strategies for cardiovascular prevention are needed that can detect high vascular risk in the absence of hyperlipidemia, that are inexpensive and simple to implement in the primary care setting, and that can provide comparable or superior effectiveness compared to currently accepted approaches.

Justification for the Use of Statin in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER): Rationale and Prespecified Analyses
In a collaborative effort involving 1315 physicians in 26 countries, the JUPITER investigators sought to determine whether statin therapy might be effective at preventing first-ever cardiovascular events among men and women at risk for vascular disease because of elevated levels of the inflammatory biomarker high-sensitivity C-reactive protein (hsCRP) but who are not candidates for statin therapy under accepted guidelines because of low-density lipoprotein cholesterol (LDLC) levels less than 130 mg/dL, the current treatment target for primary prevention.

JUPITER was a formal hypothesis testing trial based on prior observations that (1) inflammation plays a crucial role in atherogenesis; (2) that the inflammatory biomarker hsCRP independently predicts vascular events and improves global classification of risk regardless of LDLC level; (3) that statin therapy reduces hsCRP in a manner largely independent of LDLC reduction; (4) that in acute coronary syndrome as well as stable patients, the magnitude of benefit associated with statins relates in part to achieved levels of hsCRP; and (5) that in a previous hypothesis generating analysis of the AFCAPS/TexCAPS trial, no clinical benefit of statin therapy was observed among those with LDLC <150 mg/dL who had hsCRP <2 mg/L, yet a substantial clinical benefit was observed among those with LDLC <150 mg/dL who had hsCRP >2 mg/L. Thus, JUPITER was a direct test of the hypothesis raised in AFCAPS/TexCAPS - would statin therapy reduce event rates among those with elevated hsCRP but low levels of cholesterol, a group at high risk that is currently outside all treatment guidelines?

To address this public health issue, the JUPITER investigators randomly allocated 11,001 men and 6801 women who had hsCRP levels >2 mg/L (median, 4.2 mg/L) and LDLC cholesterol levels <130 mg/dL (median, 108 mg/dL) to either rosvastatin 20 mg or to placebo. All participants were followed prospectively for the primary trial end point of first-ever myocardial infarction, stroke, hospitalization for unstable angina, arterial revascularization, or cardiovascular death. All analyses were performed on an intention-to-treat basis. Additional prespecified analyses included evaluations of total mortality; the number needed to treat (NNT) to prevent 1 vascular event; whether any observed effect was attributable to LDL reduction, to CRP reduction, or to a combination of both lipid-lowering and antiinflammatory effects; and whether or not statin therapy might additionally be effective at reducing rates of deep vein thrombosis and pulmonary embolism.

What Were the JUPITER Primary Results?
The JUPITER trial was stopped early at the recommendation of its Independent Data and Safety Monitoring Board after a median follow-up of 1.9 years (maximum follow-up 5 years) because of a 44% reduction in the trial primary end point of all vascular events (P=0.00001), a 54% reduction in myocardial infarction (P=0.0002), a 48% reduction in stroke (P=0.002), a 46% reduction in need for arterial revascularization (P<0.001), and a 20% reduction in all cause mortality (P=0.02; Figure 1).

All prespecified subgroups within JUPITER significantly benefitted from rosuvastatin including those previously considered to be at “low risk” such as women, those with body
mass indices less than 25 kg/m², those without metabolic syndrome, nonsmokers, nonhypertensives, and those with Framingham Risk Scores less than 10%. Significant effects consistent with the overall trial result were also observed in the subgroup of 6375 participants with elevated hsCRP levels but no other dichotomous ATP-III risk factors (Figure 2). Of particular pathophysiologic interest, neither the absolute event rates nor the relative risk reductions within JUPITER were altered by baseline body mass index or by the presence of metabolic syndrome. These observations strongly suggest that elevated hsCRP levels, rather than other factors, are responsible for the high background event rates observed in the trial, despite very low LDL cholesterol levels.

JUPITER is also the first statin prevention trial to demonstrate clear benefits for women (hazard ratio [HR], 0.54; 95% confidence interval [CI], 0.37 to 0.80), for black and Hispanic patients (HR, 0.63; 95% CI, 0.41 to 0.98), and for the elderly (for those over age 70 years, HR, 0.61; 95% CI, 0.46 to 0.82). The JUPITER data also end controversy regarding the effects of statin therapy on all-cause mortality. Furthermore, the observation that arterial revascularization procedures were reduced by almost half suggests that the screening and treatment strategy prospectively tested in JUPITER is likely to benefit payers as well as patients.

With regard to the prespecified nonarterial end point of deep vein thrombosis or pulmonary embolism, rosuvastatin lowered the risk of this venous complication 43% (HR, 0.57; 95% CI, 0.37 to 0.86) with similar effects on both provoked and unprovoked thromboembolic events. Although JUPITER provides the first randomized trial evidence to demonstrate statin efficacy in reducing venous thrombosis, these data are consistent with prior observational studies as well as laboratory evidence suggesting nonlipid benefits of statin therapy on clotting function. There was no hemorrhagic risk of rosuvastatin in the JUPITER trial; thus, the ability to prevent deep vein thrombosis and pulmonary embolism in the absence of a bleeding risk may represent a major new approach to the prevention of this common life-threatening disorder.

Did Early Stopping Impact on the JUPITER Results?

Despite claims made by some observers, there is no credible evidence that early stopping of the JUPITER trial had any
effect on results. In fact, although the median follow-up was just less than 2 years, data accrued for those patients followed in JUPITER for between 2 and 5 years actually show a greater relative risk reduction, not a smaller estimate.

This should not be surprising as JUPITER’s Independent Data Monitoring Board (IDMB) followed rigorous principles in its prespecification that early stopping would require proof beyond reasonable doubt, and all members of the IDMB were highly experienced in monitoring clinical trials funded by both public and private entities. The IDMB viewed the JUPITER’s prespecified statistical boundary as but one component required for early closure, and although that formal statistical boundary was conservative and only evaluated after an adequate number of cases accrued, the IDMB nonetheless voted to continue JUPITER for 6 additional months. During that additional time-period, the incremental data accrued confirmed again both the magnitude and statistical significance of the apparent benefit. For those concerned that the JUPITER results somehow were a result of the play of chance, it may be of interest that the exact probability value for the trial primary end point after database closure was <0.00000001. It is thus evident that the JUPITER IDMB acted in an appropriately conservative manner to ensure a fully valid estimate of treatment effect.15

What Were the NNT Values in JUPITER?

JUPITER was a primary prevention study. Thus, as anticipated, absolute event rates in both the rosuvastatin and placebo groups were low. However, in comparison to other primary prevention trials that are commonly used to support guidelines for therapy, the absolute as well as relative risk reductions within JUPITER were quite substantial.

The NNT to prevent one clinical event is a metric of treatment benefit that encompasses both absolute and relative risk reductions and is commonly used to compare treatment strategies. When evaluating NNT values, care must be taken to specify the population under study, as well as the end points and time-frames of interest.16 Within JUPITER, which enrolled healthy men more than 50 years of age and women more than 60 years of age, the 2-, 3-, 4-, and 5-year NNT
values are 95, 49, 31, and 25, respectively for the primary trial end point, and 98, 59, 39, and 32, respectively for the restricted “hard” end point of myocardial infarction, stroke, or death (P.M.R., unpublished data, 2009). All of these NNT values compare favorably to several other therapies widely considered to be effective in the primary prevention of cardiovascular disease. For example, comparable 5-year NNT values for the treatment of hyperlipidemic men such as those enrolled in AFCAPS/TexCAPS and WOSCOPS range between 44 and 63, suggesting that the strategy of screening for elevated hsCRP is at least as effective as the strategy of screening for elevated LDLc.17

Perhaps more striking is a comparison to the treatment of hypertension where comparable 5-year NNT values between 86 and 140 have been reported as being cost-effective, or the use of prophylactic aspirin where 5-year NNT values in primary prevention exceed 300 (Figure 3). Thus, despite explicitly excluding patients with LDLc/HDL ratio >5 and including large numbers of women (who have lower event rates than do men), the absolute risk reductions observed in JUPITER and the concomitant NNT values are, if anything, superior to that of statin therapy in the primary prevention of vascular events among hyperlipidemic men or the prophylactic use of antihypertensive or antithrombotic therapies among middle-aged and older men and women.

Finally, in terms of net clinical benefit, when a composite end point of a first cardiovascular event, venous thromboembolism, or death from any cause is considered, the 5-year NNT in JUPITER was 18.13

What About Drug Safety and Incident Diabetes? Was Rosuvastatin Effective Among Trial Participants With Impaired Fasting Glucose?

Reported serious adverse events within JUPITER were equally distributed between rosuvastatin and placebo allocated participants (15.2 versus 15.5%, P = 0.6). There were no significant differences between treatment groups with regard to muscle weakness, myopathy, and hepatic or renal function. Consistent with prior statin trials, no increase in cancer was observed among those allocated to rosuvastatin despite a median on-treatment LDLc level of 55 mg/dL (and 25% of the trial having on-treatment LDLc levels less than 45 mg/dL). Although the total exposure time in JUPITER is too short to exclude long-term effects, it is reassuring that a nominally significant reduction in cancer mortality was observed among those allocated to rosuvastatin as compared to placebo (35 versus 58, P = 0.02).

With regard to developing insulin resistance and incident diabetes, the JUPITER data present a mixed picture. Overall, there was no increase in plasma glucose levels or glucosuria during follow-up, but small increases in both HbA1c (5.9 versus 5.8, P = 0.001) and physician reported diabetes (270 versus 216, P = 0.01) were observed. As with the observed reduction in cancer mortality, it is possible that this increase in diabetes represents the play of chance. However, small increases in diabetes have previously been observed in clinical trials of pravastatin, simvastatin, cerivastatin, and atorvastatin, suggesting a class effect. As shown in Figure 4, the initial hypothesis generating observation of a potential reduction in diabetes risk observed in the WOSCOPS18 trial has not been confirmed in any of 7 subsequent hypothesis testing trials.

Whether any small adverse effect of statin therapy on diabetes has clinical impact is uncertain because all diabetic patients are recommended to take statin therapy to reduce vascular event rates. Within JUPITER, 80% of all incident diabetes occurred among those who had impaired fasting glucose at study entry, a subgroup that also experienced a statistically significant reduction in the trial primary end point with a magnitude of effect consistent with the overall trial benefit. Thus, because a major concern among patients with impaired fasting glucose (as well as those with diabetes) is the prevention of myocardial infarction, stroke, and vascular death, the fact that all of these end points were favorably reduced by rosuvastatin suggests that the overall benefit-to-risk ratio was highly favorable, even for those who developed diabetes. What effect, if any, statin therapy has on microvascular disease is uncertain.

Are hsCRP Levels Stable Over Time?

Beyond demonstrating substantive absolute and relative risk reductions, the JUPITER data also provide confirmatory
evidence regarding the stability of hsCRP levels over time. Among those allocated to placebo, the intraclass correlation for repeated hsCRP measurements was 0.54, a value comparable to that of LDLC (0.55), and blood pressure (0.50) in the same study participants. These data corroborate work indicating that hsCRP levels have stability similar to that of LDLC on a month-to-month, year-to-year, and even decade-to-decade basis as has been observed in multiple prior studies. To reduce misclassification in clinical practice, neither LDLC nor hsCRP should be measured during acute stress, and both are recommended to be measured twice (preferably 2 weeks apart).

A recent multidisciplinary expert panel convened by the National Academy of Clinical Biochemistry was charged with evaluating a large series of emerging biomarkers for primary prevention of cardiovascular disease. As published in that report, “based on a thorough review of the published literature, only hsCRP met all of the criteria required for acceptance in primary prevention.” This 2009 report also reiterates that whereas levels of hsCRP >3 mg/L should optimally be repeated if a treatment recommendation is being made, levels >10 mg/L also relate to cardiovascular risk and that there is no need for extensive imaging or other tests for such patients unless abnormal history and physical examination are present.

**Was the JUPITER Benefit Attributable to LDL Reduction, to CRP Reduction, or Both?**

Current guidelines for statin therapy emphasize the need to achieve specific LDLC goals to maximize benefit. However,
Individuals with experience in the creation of clinical guidelines are now considering how the JUPITER should best be integrated into future guidelines for the prevention of cardiovascular disease. Although any new approach will be imperfect, and there will always remain a need for physicians to have flexibility with recommended therapies for individual patients, a critical issue for physicians and patients alike will be to recognize that atherothrombosis is a disorder of both lipid accumulation and inflammation.\(^2\) The clinical challenge moving forward is thus also one of physician and patient education—JUPITER not only confirms that men and women with elevated hsCRP and low LDL are at substantial vascular risk, it demonstrates that statin therapy can cut that risk by half. Simplified guidelines that advocate combined lifestyle and pharmacological therapy in those groups where trial evidence clearly supports a net benefit have the potential to greatly improve patient care and public health.

**Disclosures**

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JUPITER was designed on an a priori basis to test this hypothesis. As anticipated, lower on-treatment LDL levels and lower on-treatment hsCRP levels were both associated with significantly better clinical outcomes, even after adjusting for clinical characteristics and for baseline lipid and inflammation levels (both probability values <0.001).\(^2\) Although LDLC and hsCRP reductions were only weakly correlated in individual JUPITER patients (r values <0.15), best clinical outcomes were observed among those receiving rosvustatin who achieved low levels of both variables; in fully adjusted analyses, a 65% reduction in the hazard of vascular events was observed among those allocated to rosvustatin who achieved both LDLC <70 mg/dL and hsCRP <2 mg/L (HR, 0.35; 95% CI, 0.23 to 0.54) whereas a smaller 36% reduction in hazard was observed among those who achieved neither target (HR, 0.64; 95% CI, 0.49 to 0.84; P across treatment groups <0.0001). Moreover, a 79% relative hazard reduction was observed among those who achieved the even more aggressive targets of LDLC <70 mg/dL and hsCRP <1 mg/L (HR, 0.21; 95% CI, 0.09 to 0.51; Figure 5).\(^2\) Similar data were observed when alternative lipid fractions including the apoB/apoA ratio were substituted for LDLC, even after adjusting for all baseline clinical covariates, including entry levels of LDL, HDL, and hsCRP, as well as blood pressure, smoking status, body mass index, and family history. Thus, JUPITER prospectively demonstrates that reductions in both LDLC and hsCRP are indicators of the success of treatment with statin therapy.

**Can Guidelines for Primary Prevention Be Simplified?**

The first interventions for all patients at risk for coronary artery disease, especially those with elevated hsCRP or an elevated LDLC, must include comprehensive dietary and lifestyle advice, as well as aggressive interventions to stop smoking when present. Beyond these standard interventions, a key question remains as to when additional intervention with statin therapy is warranted. Current guidelines for primary prevention are complex, an issue that has contributed to incomplete translation of evidence into practice. In light of JUPITER, it may be possible to reduce that complexity because those with LDLC <130 mg/dL but hsCRP >2 mg/L appear to benefit from statin therapy in a manner similar to those with LDLC >160 mg/dL, the current threshold for pharmacological intervention.
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