Statins Lower Risk of First Cardiovascular Event in Patients with High C-Reactive Protein and Normal LDL Cholesterol

Ridker PM, Danielson E, Fonseca FAH, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008;359:2195–207.

Study Overview

Objective. To determine whether statin treatment can lower cardiovascular events in men and women with normal low-density lipoprotein (LDL) cholesterol and elevated C-reactive protein levels.

Design. Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER), a randomized, double-blind, placebo-controlled trial.

Setting and participants. 17,802 men (aged ≥ 50 years) and women (aged ≥ 60 years) from 1315 sites in 26 countries with LDL cholesterol < 130 mg/dL, high-sensitivity C-reactive protein (hs-CRP) level ≥ 2.0 mg/L, and triglycerides < 500 mg/dL were randomized to either rosuvastatin 20 mg daily or placebo. Patients were excluded if they were currently or had previously been on lipid-lowering therapy or were actively being treated with hormone replacement therapy; had evidence of hepatic dysfunction, a creatine kinase level ≥ 3 times the upper limit of normal, serum creatinine level ≥ 2.0 mg/dL; a recent history of alcohol or drug abuse, cancer within 5 years, diabetes, uncontrolled hypertension or hypothyroidism, or an inflammatory disorder such as severe arthritis, inflammatory bowel disease, or lupus; or were on immunosuppressant therapy. Patients were included in the final sample if they had 80% compliance during a 4-week placebo run-in period. At enrollment, the median LDL level was 108 mg/dL in both arms, and hs-CRP levels were 4.2 and 4.3 mg/L in the rosuvastatin and placebo arms, respectively.

Main outcome measure. Combined primary endpoint of any cardiovascular event, including myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes.

Main results. The trial was stopped short of the planned 4 years of follow-up because the prespecified number of primary endpoints in the trial was reached earlier than expected. After a median follow-up of 1.9 years, patients in the rosuvastatin group had a 44% lower rate of the combined endpoint than the placebo group (0.77 vs. 1.36 person-years of follow-up, respectively; hazard ratio [HR], 0.56 [95% confidence interval {CI}, 0.46–0.69]; $P < 0.001$). The trend for a reduced rate of cardiovascular outcomes was evident for each of the individual outcomes as well, including death from cardiovascular causes (HR, 0.53 [95% CI, 0.40–0.69]; $P < 0.001$) and death from any cause (HR, 0.80 [95% CI, 0.67–0.97]; $P = 0.02$). Rosuvastatin decreased LDL cholesterol by 50% and hs-CRP by 37%. After 12 months of follow-up, the median LDL cholesterol and hs-CRP levels were 55 mg/dL and 2.2 mg/L in the rosuvastatin arm as compared with 110 mg/dL and 3.5 mg/L in the placebo arm. Triglycerides were also significantly lower in the rosuvastatin group at 1 year (99 mg/dL vs. 119 mg/dL). No increase in myopathy or cancer was noted in the rosuvastatin group, although there was a higher incidence of physician-reported diabetes.

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Conclusion. In patients with high hs-CRP and normal LDL cholesterol, rosuvastatin treatment lowers the risk of major cardiovascular events.

Commentary

Extensive research has documented an association between elevated hs-CRP levels and an increased risk for cardiovascular events [1–6]. However, no randomized trial had yet explored the benefit of an hs-CRP–based treatment strategy for the primary prevention of cardiovascular events. The JUPITER trial fills this void. Participants were enrolled only if their hs-CRP level was high (≥ 2 mg/L) and LDL level was less than 130 mg/dL, the LDL level that would normally serve as a threshold for considering statin treatment for primary prevention. The trial was designed to be terminated after the occurrence of a prespecified number of cardiovascular events, but the termination point was reached at least 2 years prior to the expected length of the trial. The trial was diverse by design, and 25% of participants were either African American or Hispanic.

Results showed a clear benefit in the rosuvastatin group, with a 44% lower risk of a first cardiovascular event. Analyses of secondary endpoints (each component of the combined primary endpoint) and subgroup analyses showed a robust risk reduction in cardiovascular events in patients treated with rosuvastatin. The number needed to treat to prevent an initial cardiovascular event after 2 years with rosuvastatin was 95. The absolute risk reduction (from 0.77 events to 1.36 per 100 person-years of follow-up in the rosuvastatin vs. placebo group) was rather small because most patients were relatively healthy.

The findings of JUPITER may prompt new recommendations to lower the threshold LDL cholesterol level at which to initiate statin treatment in a relatively low-risk population. However, several critiques of this study have emerged, providing some ambiguity about whether hs-CRP testing has a role in guiding treatment decisions. In an accompanying editorial, Hlatky [7] recommends caution in interpreting these results, explaining that JUPITER was not a randomized trial of hs-CRP measurement but rather a trial of statin therapy with entry criteria based on hs-CRP. The trial did not include control subjects with low hs-CRP levels to help determine whether low-risk patients (based on both LDL cholesterol and hs-CRP) also could benefit from statins. Furthermore, the early stoppage of the trial precluded collection of data on the risk of long-term lowering of LDL levels.

Recent evidence also has called into question the role of CRP as a potential causative factor in ischemic vascular disease. Zacho and colleagues [8] used genetic and outcomes data of 4 separate datasets (a prospective cohort, a cross-sectional study, and 2 case-control studies) to assess whether 4 genetic polymorphisms associated with elevated CRP levels were associated with ischemic vascular events. The authors found a clear association between elevated CRP levels and vascular events, and subjects with documented evidence of the CRP-related genetic polymorphisms had much higher CRP levels than those without the polymorphisms. However, there was no association between the presence of a polymorphism and ischemic events. This evidence suggests that CRP may be associated with ischemic events but does not appear to be part of the causal pathway.

In a 2003 report, the American Heart Association (AHA) and the Centers for Disease Control and Prevention (CDC) recommended a limited role for hs-CRP testing [9], specifically that hs-CRP testing be considered an aid in treatment decisions for patients not deemed clear candidates for statin treatment with an intermediate risk for a cardiovascular event (10%–20% risk of an event in 10 years as measured by the Framingham Risk Score). The AHA and CDC also recommended that hs-CRP testing be used to help determine risk for recurrent events in patients with stable coronary disease or acute coronary syndromes.

The JUPITER trial has provided a clear advancement in the field of cardiovascular primary prevention, and more aggressive treatment with statins will likely emerge as a recommendation in the wake of this study. However, the specifics of these recommendations are not yet clear. Regarding hs-CRP testing, the AHA/CDC recommendation of limited use still seems prescient until further research can confirm the clear benefit of measuring hs-CRP. Of note, AstraZeneca, the manufacturer of rosuvastatin, funded the JUPITER study and aided in data collection but did not participate in the analysis or writing the manuscript.

Applications for Clinical Practice

Healthy patients with normal LDL cholesterol levels may benefit from statins for primary prevention of cardiovascular events. Further research is required to determine exactly who should be treated, the target LDL cholesterol levels for treatment, and to confirm the assumption that benefits seen with rosuvastatin in this study can be realized with other statins as well (ie, class effect). hs-CRP testing remains an option to aid in treatment decision making for some patients who are borderline candidates for treatment.

—Review by Jason P. Block, MD, MPH

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