CRITICAL CARE

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To JUPITER and beyond: Statins, inflammation, and primary prevention

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Expanded Abstract

Citation

Ridker PM, Danielson E, Fonseca FAH, Genest J, Gotto AM, Kastelein JJP, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ: Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein. *NEJM* 2008, 359: 2195-2207 [1].

Background

Increased levels of the inflammatory biomarker high-sensitivity C-reactive protein predict cardiovascular events. Since statins lower levels of high-sensitivity C-reactive protein as well as cholesterol, we hypothesized that people with elevated high-sensitivity C-reactive protein levels but without hyperlipidemia might benefit from statin treatment.

Methods

Objective: To investigate whether treatment with rosuvastatin, 20 mg daily, as compared to placebo, would decrease the rate of first major cardiovascular events.
Design: Randomized, double-blind, placebo-controlled, multicenter trial.
Setting: 1315 sites in 26 countries.
Subjects: 17,802 apparently healthy men and women with low-density lipoprotein (LDL) cholesterol levels of less than 130 mg per deciliter (3.4 mmol per liter) and high-sensitivity C-reactive protein levels of 2.0 mg per liter or higher.
Intervention: Subjects were randomly assigned to rosuvastatin, 20 mg daily, or placebo.
Outcomes: The primary outcome was the occurrence of a first major cardiovascular event, defined as myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes. Secondary endpoints included the components of the primary end point considered individually as well as death from any cause.

Results

The trial was stopped after a median follow-up of 1.9 years (maximum, 5.0). Rosuvastatin reduced LDL cholesterol levels by 50% and high-sensitivity C-reactive protein levels by 37%. The rates of the primary end point were 0.77 and 1.36 per 100 person-years of follow-up in the rosuvastatin and placebo groups, respectively (hazard ratio for rosuvastatin, 0.56; 95% confidence interval [CI], 0.46 to 0.69; P<0.00001), with corresponding rates of 0.17 and 0.37 for myocardial infarction (hazard ratio, 0.46; 95% CI, 0.30 to 0.70; P=0.0002), 0.18 and 0.34 for stroke (hazard ratio, 0.52; 95% CI, 0.34 to 0.79; P=0.002), 0.41 and 0.77 for revascularization or unstable angina (hazard ratio, 0.53; 95% CI, 0.40 to 0.70; P<0.00001), 0.45 and 0.85 for the combined end point of myocardial infarction, stroke, or death from cardiovascular causes (hazard ratio, 0.53; 95% CI, 0.40 to 0.69; P<0.00001), and 1.00 and 1.25 for death from any cause (hazard ratio, 0.80; 95% CI, 0.67 to 0.97; P=0.02). Consistent effects were observed in all subgroups evaluated. The rosuvastatin group did not have a significant increase in myopathy or cancer but did have a higher incidence of physician-reported diabetes.

Conclusions

In this trial of apparently healthy persons without hyperlipidemia but with elevated high-sensitivity C-reactive protein levels, rosuvastatin significantly reduced the incidence of major cardiovascular events. (ClinicalTrials.gov number, NCT00239681.)

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Commentary

It is well known that statins reduce the risk of myocardial infarction, stroke, and death from cardiovascular events in patients with established vascular disease and in those with risk factors, such as diabetes or hyperlipidemia. Yet, half of all myocardial infarctions and strokes occur among otherwise healthy men and women without known vascular disease or risk factors [1]. Inflammation is thought to play a central role in the development and progression of vascular disease. In addition to their lipid-lowering effects, statins have anti-inflammatory properties, reducing levels of high-sensitivity C-reactive protein (hsCRP), an acute-phase protein found in the blood that rises in response to inflammation. HsCRP level is a stronger predictor of cardiovascular events than the LDL cholesterol level and that it adds prognostic information to that conveyed by the Framingham risk score [2]. What is not known, however, is whether statins might also benefit patients with evidence of inflammation but without vascular disease or hyperlipidemia.

The Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial was designed to look at the effects of rosuvastatin in healthy patients with elevated hsCRP levels but without hyperlipidemia [1]. It was conducted in 1315 sites in 26 countries and financially supported by AstraZeneca, the makers of rosuvastatin. Between 2003 and 2006, over 17,000 subjects were enrolled with a mean follow-up time of 1.9 years. As expected, treatment with rosuvastatin reduced LDL and hsCRP levels significantly. Rosuvastatin reduced the primary endpoint of a first major cardiovascular event (absolute risk 1.6% vs. 2.8%, hazard ratio 0.56, $p<0.00001$) as well as all secondary endpoints with the exception of hospitalization for unstable angina. The number needed to treat to prevent the occurrence of one primary endpoint in 2 years was 95, dropping to 31 for 4 years, and 25 for 5 years of therapy. Results of the study were consistent across clinically important subgroups. Total adverse events did not differ between groups. Muscle weakness, stiffness, or pain was fairly common but did not differ between groups (16.0% vs. 15.4%, rosuvastatin vs. placebo, $p=0.34$). Myopathy was uncommon (<0.1%) and only a single case of rhabdomyolysis occurred, this in a 90-year old subject with influenza, pneumonia, and trauma-induced myopathy. Interestingly, physician-reported diabetes was more frequent in the rosuvastatin group.

This was a very large, well-conducted study using clinically meaningful endpoints which may expand the use of statins for primary prevention to new patient populations. A few limitations deserve mention. At baseline characteristics, patients were not entirely free of risk prior to randomization. Patients were overweight (median body-mass index 28) and over 40% had features of the metabolic syndrome. Furthermore, 16% were current smokers and 11% had a family history of premature coronary heart disease. Even so, prevalence of these risk factors actually increases the generalizability of this study, given their frequency in Western societies. The study did not include people with low levels of hsCRP and therefore does not address the use of statins in patients without evidence of inflammation. However, as the authors note their prior work showed extremely low event rates and no evidence that statin therapy lowered vascular risk among healthy subjects with neither hyperlipidemia nor elevated hsCRP levels [3].

Statins, like many preventative measures, must be taken for years before yielding a benefit. If guidelines were expanded to address C-reactive protein, it is estimated that an additional 6 to 8 million adults in the United States would have a statin indication based on JUPITER inclusion criteria [4]. Though not without cost, statin therapy is this patient population would be cost-effective, with a cost per quality adjusted life-year (QALY) of $40,457, well below the traditional cutoff of $50,000 per QALY [4].

Other than general medical interest, one might ask why this study would appeal to the intensivist. The anti-inflammatory and anti-thrombotic properties of statins have prompted speculation that they may be useful in the treatment or prevention of severe sepsis [5], a syndrome characterized by dysregulation of inflammation, coagulation, and other acute phase responses. In murine models of sepsis, statins improve survival [6-8]. A variety of observational studies in humans have examined the role of statins in the prevention or treatment of infection and sepsis, as recently reviewed [9]. Most suggest a clinical benefit for statins, yet others show no benefit, and one shows possible harm. Based on these findings, several randomized trials of statins in infection are either planned, underway, or recently completed [10-21]. Unfortunately, these are small studies that are underpowered to address mortality or other clinically meaningful endpoints, with their primary endpoints focusing on inflammatory cytokines and markers of endothelial function. In addition to their potential *before* or *during* severe infection, one study highlights the potential for statins *after* infection. In subjects who survived an initial hospitalization for community-acquired pneumonia, circulating IL-6 concentrations at hospital discharge were higher among subjects who subsequently died of cardiovascular diseases [22], raising the possibility of statin use to mitigate the effects of ongoing subclinical inflammation after hospitalization for infection.

Recommendation

Statins reduced risk of first major cardiovascular event in healthy subjects with elevated hsCRP but without

hyperlipidemia. Furthermore, their use appears to be cost-effective from a societal perspective. Even so, society may wish to focus on aggressive reduction of traditional risk factors (obesity, hypertension, diabetes) before broadly increasing statin use. Though the results of statin trials in infection and severe sepsis are anxiously anticipated, larger studies will be needed before statins are routinely recommend in the management of severe infections.

Competing interests
The authors declare no competing interests

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