Elevated C-Reactive Protein and Vascular Events

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Related To: Chapter 23. Hyperlipidemia

Current treatment guidelines for primary and secondary prevention of cardiovascular disease recommend statin therapy for patients with established vascular disease, diabetes, dyslipidemia and elevated risk based on the Framingham risk prediction model. However, more than half of all myocardial infarctions and strokes occur among apparently healthy men and women with levels of low-density lipoprotein (LDL) at or below current target levels. High-sensitivity C-reactive protein (hsCRP) is an inflammatory biomarker that independently predicts future vascular events regardless of LDL level.

The JUPITER study (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) was a randomized, double-blind, placebo-controlled trial of rosuvastatin 20 mg per day versus placebo in 17,802 apparently healthy men and women with LDL values less than 130 mg/dL and hsCRP levels of 2.0mg/L or greater for a median follow-up of 1.9 years.[1] The combined primary endpoint was the occurrence of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes. The trial was planned for 5 years but was stopped prematurely due to the primary endpoint being met early.

Patients were well matched at baseline with no significant differences noted between rosuvastatin and placebo (see Table 1).

Table 1. Median Baseline Characteristics of Trial Participants.

Characteristic	Rosuvastatin (N=8901)	Placebo (N=8901)
Age, yr.	66.0	66.0
SBP, mmHg	134	134
DBP, mmHg	80	80
hsCRP, mg/L	4.2	4.3
Total cholesterol, mg/dL	186	185
LDL cholesterol, mg/dL	108	108
HDL cholesterol, mg/dL	49	49
Glucose, mg/dL	94	94

LDL and hsCRP were significantly and consistently reduced with rosuvastatin throughout the follow-up period with reductions averaging approximately 50% for both (see Table 2).

Table 2. Median Lipid and hsCRP Levels during Follow-up.

Level	12 Mo.		24 Mo.		36 Mo.		48 Mo.	
	Rosuvastatin	Placebo	Rosuvastatin	Placebo	Rosuvastatin	Placebo	Rosuvastatin	Placebo
hsCRP, mg/L	2.2	3.5	2.2	3.5	2.0	3.5	1.8	3.3
LDL, mg/dL	55	110	54	108	53	106	55	109
HDL, mg/dL	52	50	52	50	50	49	50	50

The combined primary end point occurred at a rate of 0.77/100 person years in the rosuvastatin group versus 1.36/100 person years in the placebo group for a hazard ratio of 0.56 (95% CI 0.46-0.69). This represents a 44% relative risk reduction, which is highly statistically significant (<0.00001). All other individual end points (e.g., myocardial infarction, stroke) were significantly reduced with the exception of hospitalization for unstable angina (p=0.09). In subgroup analysis, there were no differences among any subgroups (e.g., sex, age, race, hypertension) for subjects receiving rosuvastatin or placebo. Adverse events were no more common with rosuvastatin than with placebo except for newly diagnosed diabetes that was slightly more common with rosuvastatin (3.0% vs. 2.4%). Muscular weakness, stiffness, pain, myopathy and rhabdomyolysis occurred at similar rates for rosuvastatin and placebo.

Although the results of the JUPITER trial are impressive and positive news for statins in primary prevention, there are limitations to this trial. Patients enrolled in JUPITER would not qualify for treatment using the National Cholesterol Education Program Adult Treatment Panel III guidelines that are now quite dated (published in 2001). The findings of JUPITER suggest that more aggressive treatment especially for primary prevention in patients who otherwise appear healthy but have a biomarker for inflammation is in order and would greatly expand the number of patients potentially eligible for treatment. Although the planned follow-up in JUPITER was 5 years, the study was stopped at 1.9 years, thereby limiting the amount of information about the long-term safety of rosuvastatin and the wisdom of achieving quite low LDL levels. The authors claim that the risk reduction observed in JUPITER was greater than expected on the basis of previous trials, but early termination of the study may exaggerate these results to some degree. Furthermore, the routine use of hsCRP as a screening tool for risk assessment is not currently recommended. However, the results of the JUPITER trial are likely to have a major impact on the acceptability of routine screening with hsCRP.

1. 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;359:2195-2207.