Rosuvastatin Reduces Primary Cardiovascular Events in Apparently Healthy Individuals with Elevated C-Reactive Protein Levels

This large prospective study is the first to show that statin therapy can prevent cardiovascular (CV) events among individuals who do not have elevated lipid levels. The JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; NCT00239681) trial demonstrated that rosuvastatin 20 mg significantly reduced the rate of primary CV events in an apparently healthy population that had normal low-density lipoprotein (LDL) levels but elevated high-sensitivity C-reactive protein (hsCRP) levels. A maximum follow-up of 5 years had been planned for the study, but the data and safety monitoring committee stopped the trial early (in March 2008) due to an overwhelming benefit of rosuvastatin.

The double-blind, multicenter trial included 17,802 individuals who had no history of CV disease or diabetes and a normal LDL level (<130 mg/dL) but a high hsCRP level (≥2 mg/L). The age criterion was ≥50 years for men and ≥60 years for women. Approximately 38% of the study population was female and approximately 25% was black or Hispanic.

Patients were randomly assigned to receive either rosuvastatin 20 mg daily (8901 patients) or placebo (8901 patients). The primary endpoint was the occurrence of a first major CV event, defined as nonfatal myocardial infarction (MI), nonfatal stroke, hospitalization for unstable angina, revascularization procedures, or confirmed death from CV causes.

Paul Ridker, MD, Brigham and Women's Hospital, Boston, MA, the lead author of the study, reported that at a median follow-up of 1.9 years, 142 events had occurred in the rosuvastatin group, compared with 251 in the placebo group, for a rate of 0.77 versus 1.36 per 100 person-years of follow-up (HR, 0.56; 95% CI, 0.46 to 0.69; p<0.00001). Dr. Ridker noted that the number that was needed to treat to prevent the occurrence of 1 primary endpoint was 25 over a 5-year treatment period. This number is lower than that associated with treating hyperlipidemia in primary prevention, he said.

Rosuvastatin also was associated with lower rates of the prespecified secondary endpoints, which included the individual components of the composite endpoint, as well as death from any cause (Table 1). Dr. Ridker said that all-cause mortality was driven largely by CV events.

Table 1. Effect of Rosuvastatin on Primary Endpoints in JUPITER Trial.[a]

Endpoint	Rosuvastatin	Placebo	Significance
Primary composite endpoint[b]	0.77	1.36	HR=0.56; 95% CI, 0.46-0.69; p<0.00001
Nonfatal MI	0.12	0.33	HR=0.35; 95% CI, 0.22-0.58; p<0.00001
Nonfatal stroke	0.16	0.31	HR=0.52; 95% CI, 0.33-0.80; p=0.003
Revascularization or hospitalization for unstable angina	0.41	0.77	HR=0.53; 95% CI, 0.40-0.70; p<0.00001
All-cause mortality	1.00	1.25	HR=0.80; 95% CI, 0.67-0.97; p=0.02

[a]Results are given as the rate per 100 person-years of follow-up.

[b]The primary endpoint was defined as the occurrence of a first major CV event (nonfatal MI, nonfatal stroke, hospitalization for unstable angina, a revascularization procedure, or confirmed death from CV causes).

The benefit of rosuvastatin was consistent across several prespecified subgroups that were classified by baseline characteristics, such as age, sex, race, body-mass index, and smoking history. Among individuals who had an elevated hsCRP level (> 2 mg/L) and no other major risk factor (other than older age), the benefit of rosuvastatin was similar to that for individuals at higher risk (HR, 0.63; 95% CI, 0.44 to 0.92; p=0.01).

Rosuvastatin significantly reduced levels of hsCRP and LDL throughout the duration of the trial. At 4 years, the median hsCRP levels were 1.8 mg/L and 3.3 mg/L in the rosuvastatin and placebo groups, respectively (p<0.001); the corresponding median LDL levels were 55 mg/dL and 109 mg/dL (p<0.001).

Treatment with rosuvastatin appeared to be safe, as evidenced by a similar rate of serious adverse events in the 2 groups (15.2% vs 15.5%; p=0.60), including similar rates of myopathy (10 vs 9 cases), ALT elevation >3x ULN (23 vs 17), and newly diagnosed cancer (298 vs 314; p=NS for all). Deaths from cancer were lower with rosuvastatin (0.4% vs 0.7%; p=0.02). There was a higher incidence of physician-reported diabetes in the rosuvastatin group (3.0% vs 2.4%; p=0.01), a finding that was similar to that seen in other major statin trials.

The study results raise an important question: Should the indications for statin therapy be expanded? Dr. Ridker noted that expert panels will need to evaluate the results to determine whether screening guidelines should be modified.

A report on the study and an accompanying editorial were published in the November 20, 2008 issue of *The New England Journal of Medicine* and are available online (www.nejm.org).

Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH)

Results of the SEARCH (NCT00124072) trial did not show a significant clinical benefit with simvastatin 80 mg versus 20 mg and failed to find any cardiovascular benefit of large doses of folic acid.

Rory Collins, MD, University of Oxford, Oxford, UK, presented the SEARCH results at the American Heart Association meeting in New Orleans.

It is generally accepted that the use of statin therapy to lower low-density lipoprotein cholesterol (LDL-C) levels can reduce the risk of heart attack, stroke, or a revascularization procedure; however, there has been some uncertainty as to how intensively LDL-C levels should be lowered.

SEARCH was the largest randomized trial and had the longest follow-up of any study that directly assessed the efficacy and safety of more- versus less-intensive LDL-C-lowering. The primary study outcome was major vascular events (MVEs; defined as nonfatal myocardial infarction (MI), coronary/noncoronary revascularization, death from coronary heart disease, or stroke). The study population of SEARCH included 12,064 subjects (mean age 64 years; 10,012 men; 2052 women) with a prior history of MI for whom statin therapy was indicated. Mean LDL-C at baseline was 97 mg/dL (2.5 mmol/L). Subjects were randomly assigned to receive either the standard 20 mg/day dosage of simvastatin (n=6033) or 80 mg/day simvastatin (n=6031).

After a mean of 6.7 years of treatment, LDL-C was on average 14% (14 mg/dL; 0.35 mmol/L) lower in the 80 mg group versus those who received standard therapy. The reduction was associated with 6% fewer heart attacks, strokes, or revascularizations.

Although the difference between the 2 dosage groups was not significant, when the data from SEARCH were combined in a meta-analysis with data from 4 other studies of more versus less lipid-lowering [Cannon CP et al. *N Engl J Med* 2004; de Lemos JA et al. *JAMA* 2004; LaRosa JC et al. *N Engl J Med* 2005; Pedersen TR et al. *JAMA* 2005], lowering LDL-C further by an average of 20 mg/dL was shown to produce a 15% further reduction in MVE (Figure 1).

Figure 1. CTT Meta-Analysis: Effects of Statin on Major Vascular Event per mmol/L LDL-C Reduction.