



## **The JUPITER Study: Forget LDL Cholesterol, Statins for Everyone?**

*By Cathy H. Turner, Pharm.D.*

The results of the JUPITER study were published in the November 20<sup>th</sup> issue of the *New England Journal of Medicine*.<sup>1</sup> Once again [See *Inquiry* 2008;1(5)1-2.], the absolute predictive value of LDL cholesterol for risk of cardiac disease is called into question. Is it the drug or the cholesterol level that affects cardiovascular risk, or now, should we consider high-sensitivity C-reactive protein as a predictor of disease? JUPITER does not answer all of these questions, and despite extrapolation by the media, it was not designed to do so.

In this trial, women age 60 y and over and men 50 y and over with LDL cholesterol less than 130 mg/dL, no cardiovascular risk factors, and high-sensitivity C-reactive protein greater than 2mg/L were randomly assigned to receive rosuvastatin 20 mg daily or placebo. Of the 89,890 patients screened for study inclusion, 19,323 met inclusion and exclusion criteria. With approximately 78% of patients excluded from study participation, these study results cannot be applied to a broad patient population. The primary reasons for exclusion were LDL cholesterol greater than 130 mg/dL (52%) and high-sensitivity C reactive protein less than 2 mg/dL (36%). Other clinical reasons for exclusion occurred in 1% or less of screened patients and were as follows: diabetes, hypothyroidism, liver disease, triglycerides > 500 mg/dL, age, current use of hormone replacement therapy, or history of cancer in the past five years.<sup>1</sup>

The primary endpoint was occurrence of first major cardiovascular event defined as nonfatal myocardial infarction, nonfatal stroke, and hospitalization for unstable angina, an arterial revascularization procedure, or death from cardiovascular causes. All patients were required to complete a 4-week placebo run-in phase to ensure adequate compliance defined as taking more than 80% of study tablets. After the run-in phase, 17,802 patients entered the study. The study monitoring board stopped the trial early due to a decreased event rate in the rosuvastatin group. At study termination, 142 events had occurred in the rosuvastatin group compared to 251 events in the placebo group (hazard ratio, 0.56; 95% confidence interval, 0.46 – 0.69; P<0.00001).<sup>1</sup> While this difference is statistically significant, an editorialist<sup>2</sup> points out that absolute differences in risk are more clinically relevant than relative differences. He notes that the proportion of patients with hard cardiac events was decreased from 1.8% in the placebo group (157 of 8901) to 0.9% in the rosuvastatin group (83 of 8901). Based on this absolute risk reduction, 120 people would need to be treated for 1.9 years to prevent one event.<sup>2</sup>

Rosuvastatin's ability to reduce LDL-cholesterol is well-established. At 12, 14, 36, and 48 months the median LDL-cholesterol ranged from 53 mg/dL to 55 mg/dL for the rosuvastatin group compared to 106 to 110mg/dL for the placebo group. The ranges of median high-sensitivity C-reactive protein at the same time periods were 1.8–2.2mg/L for the rosuvastatin group and 3.3–3.5mg/L for the placebo group. The inter-group

comparisons for LDL-cholesterol and high-sensitivity C-reactive protein were statistically significant.<sup>1</sup> Despite the statistical differences, the clinical importance is not clear. Since high-sensitivity C-reactive protein is not routinely monitored or used to guide therapy, the importance of maintaining a lower level over time is not known. Additionally, the long-term effect of extraordinarily low LDL-cholesterol levels such as 55 mg/dL is also unknown.<sup>2</sup>

A slight but statistically significant difference in glycated hemoglobin was seen between groups; the median glycated hemoglobin was 5.8% in the rosuvastatin group and 5.8% in the placebo group (p=0.001). A more concerning finding was the frequency of physician-reported diabetes which occurred in 3% (270 of 8901) of rosuvastatin-treated patients and in 2.4% (216 of 8901) of placebo-treated patients (p=0.01). The diagnosis of diabetes was not adjudicated by the end-point committee and was, therefore, left to the opinion of the attending physician.<sup>1</sup> However, diabetes is not a rare or loosely-defined disease state lending itself to misdiagnosis. It is possible that causality may have been debatable and that blinded review would have been valuable for this reason.

#### **What Does This Mean for Patient Care?**

Since LDL cholesterol and high-sensitivity C reactive protein levels were the reason for exclusion for 88% of patients who were not admitted to the JUPITER trial and the patient age was restricted to greater than 60 y or 50 y for women and men, respectively, broad application of these study results is inappropriate. Additionally, the increased incidence of diabetes in the rosuvastatin group is concerning and cannot be overlooked. Diabetes is a risk factor for cardiovascular disease in its own right. While the study results indicated a cardioprotective effect of rosuvastatin, it is not known if the long-term

effect of an increased incidence of diabetes would out-weigh this benefit. The long-term effects of ultra low LDL-cholesterol levels are unknown and the risks of elevated C-reactive protein are not well defined. Risking all of these unknowns does not seem worth the minimal gain of a 0.9% absolute risk reduction for hard cardiac endpoints. Statins can stay on the shelf a little while longer for patients with no cardiovascular disease and LDL-cholesterol less than 130 mg/dL.

#### **References**

1. Ridker PM, Danielson E, Fonseca FAH, Genest J, Gotto AM, Kastelein JJP, et al. Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein. *NEJM*. 2008;359:2195-207.
2. Hlatky MA. Expanding the Orbit of Primary Prevention – Moving beyond JUPITER. [editorial] *NEJM*. 2008;359:2280-2.

### *Program Announcement*

---

#### **Sodium Chloride vs. Sodium Bicarbonate for Hydration to Prevent Contrast-Media Induced Nephropathy: A Review of the Literature**

**Inman, Room 202**

**9:00 AM**

**December 17<sup>th</sup>, 2008**

**Sarah Bradley, Pharm.D.**

Pharmacy Practice Resident  
Saint Thomas Hospital

---

*Light refreshments will be served.*