Blue Cross and Blue Shield of New Mexico

The JUPITER Trial

The JUPITER trial attempts to answer this perturbing question: “Why do half of all myocardial infarctions and strokes occur in apparently healthy men and women with levels of LDL that are below currently recommended thresholds of treatment?” The study addresses the biomarker high-sensitivity C-reactive proteins (hs-CRP), an inflammatory marker that has long been linked to an increased risk of adverse cardiovascular events. While cholesterol has been a target for decreasing cardiovascular risk, physicians have known less what to do about elevated hs-CRPs, using it more as a harbinger of trouble, than as an indication for action. Statins have been previously shown to decrease levels of hs-CRP as well as lipids, and the magnitude of the benefit of statin therapy is known to be in part due to its lowering of hs-CRP. However, while we have guidelines for lowering cholesterol, lowering hs-CRP alone has not been a target of therapy. The study, sponsored by AstraZeneca, took individuals who did not have elevated LDL by current treatment guidelines, but did have elevated hs-CRP, treated them with rosuvastatin (CRESTOR), and then monitored them for major first-time cardiovascular events.

The study randomly assigned 17,802 patients with low LDL levels (<130mg/deciliter) but elevated hs-CRP (2.0 mg/liter or higher), to receive either 20 mg of rosuvastatin (CRESTOR) daily or placebo. Men above the age of 50 and women above the age of 60 with these criteria were eligible. Among the exclusion criteria were history of lipid-lowering therapy, hormone replacement therapy, diabetes, and blood pressure >190 mmHg systolic or >100 mmHg diastolic. Additional criteria included alanine aminotransferase greater than twice the upper limit of normal, serum creatinine >2 mg/dL (176.8 micromol/L), and TSH >1.5 times the upper limit of normal. Patients, who had cancer within the previous five years (except basal cell or squamous cell skin cancer), patients with inflammatory diseases (e.g., rheumatoid arthritis, inflammatory bowel disease) and patients taking immunosuppressants (e.g., corticosteroids, cyclosporine) were also excluded. The primary outcome measured was major cardiovascular events (MI, stroke, hospitalization for angina or revascularization, or cardiac death). The study was planned to continue for five years and/or until 520 events had occurred.

When a prespecified interim efficacy analysis was performed after less than two years, the trial was terminated given the markedly beneficial results of the statin. For example, after one year of therapy, the rosuvastatin group had a 50% lower average LDL (108 to 55) and a 37% (4.2 to 2.2) lower hs-CRP level as compared with the placebo group. At the time of the termination of the study, 142 first major cardiovascular events had occurred in the rosuvastatin group as compared with 251 in the placebo group. Rosuvastatin also decreased the number of deaths from any cause (hazard ratio for the rosuvastatin group, 0.80; 95% CI, 0.67 to 0.97; P=0.02). With Kaplan-Meir estimates, the number of patients needed to treat with rosuvastatin for 2 years in order to prevent one primary endpoint is 95, and if the risk is projected over a 5 year period, the number needed to treat to prevent the occurrence of one primary endpoint, is 25.

Some questions remain to be addressed. Guidelines currently do not recommend routine use of hs-CRP as a screening test for the general population. Rather, it is recommended for clarifying treatment goals or motivating patients with multiple risk factors. A patient with an LDL <130 mg/dL with more than two risk factors (i.e., smoking, hypertension, low HDL, family history, age) would be an example of a patient who might benefit from checking an hs-CRP. Certainly, current guidelines will need to be reassessed based on the JUPITER study results.

Previous statin primary prevention studies included patients at higher risk than those studied in the JUPITER trial. JUPITER demonstrates that statins are effective for primary prevention of cardiovascular

events in a relatively low-risk population we would not currently consider for statin therapy. But long-term risks and costs may outweigh the benefits for most patients who are similar to those included in JUPITER. Keep in mind that about 80% of screened patients were excluded from study entry largely because of LDL levels above 130 mg/dL or hs-CRP levels less than 2 mg/L.

Finally, less than 50% of patients who could benefit from lipid-lowering therapy based on current guidelines are receiving it. Additionally, only about half of patients prescribed lipid-lowering therapy are taking it six months later because of poor compliance. The direct and indirect costs of unused statin prescriptions in high-risk populations is likely staggering. Until the current guidelines are updated to reflect this information, one recommendation would be to identify patients who are candidates for statins based on current guidelines, and encourage adherence.

For further information or questions pertaining to this newsletter, e-mail Richard Reynolds at Richard_g_reynolds@bcbsnm.com.

References:

1. Bragin, I. Breaking News: The Jupiter Trial. Clinical Correlations – NYU Internal Medicine Blog – A dose of Medicine (Internet)
2. 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.
3. Rosuvastatin (CRESTOR) for high C-reactive protein. Pharmacist's Letter/Presciber's Letter 2008; 24(12): 241201.