Relaxin improved clinical outcomes following hospital discharge as well. Compared with placebo, relaxin 30 µg/kg reduced the risk of cardiovascular death or rehospitalization due to heart failure or renal failure by 87% at 60 days (HR, 0.13; p=0.053). No patients died because of cardiovascular causes in the Relaxin 30 µg/kg group at 180 days (p<0.05).

Relaxin had a favorable safety profile, with a similar proportion of patients reporting any adverse event in the placebo and relaxin groups. Compared with placebo, relaxin 30 µg/kg was associated with a nonsignificant increase in the incidence of bronchitis (0 vs 2.4%), stroke (1.6% vs 4.8%), renal failure (1.6% vs 2.4%), and hypotension (9.8% vs 11.9%). No cases of severe hypotension were reported in the placebo or relaxin 30 µg/kg groups, though 2 cases (4.1%) were reported in the relaxin 250 µg/kg group. Relaxin 250 µg/kg, but not 30 µg/kg, was associated with a nonsignifcant doubling in the incidence of worsening renal dysfunction (≥0.3 mg/dL increase in serum creatinine) compared with placebo (15% vs 7%, p=0.19).

Based on these findings, Dr. Teerlink and colleagues have chosen the 30 µg/kg dose for evaluation in the upcoming international phase 3 trial of relaxin in acute heart failure (RELAX-AHF-1).

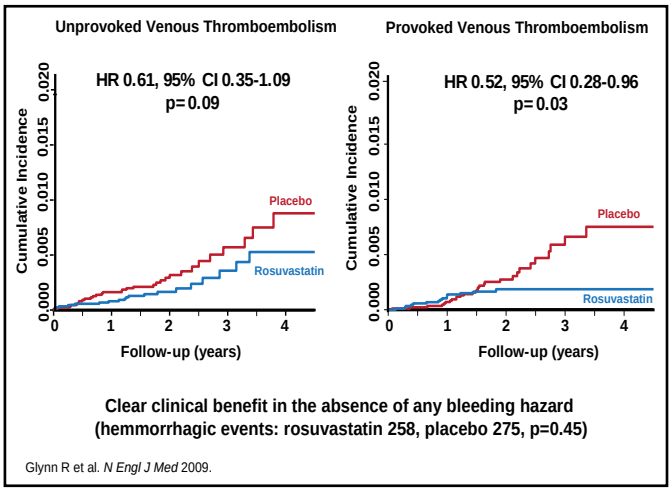
JUPITER Study Continues to Make News

A number of presentations highlighted new analyses from the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER; NCT00239681) study, the results of which are expected to have a significant impact on the screening and treatment of cardiovascular disease (CVD). JUPITER was a primary preventive, prospective, randomized trial that included 17,802 men (aged ≥50 years) and women (aged ≥60 years) with no CVD or diabetes mellitus, and low-density lipoprotein (LDL) cholesterol and high-sensitivity C-reactive protein (hsCRP) levels <130 mg/dL and ≥2 mg/L, respectively. Subjects received either rosuvastatin (20 mg/day) or placebo. The trial was stopped prematurely after a median follow-up of 1.9 years due to clear and significant treatment benefits, wherein rosuvastatin produced a 44% reduction in the primary study endpoint (cumulative incidence rate of myocardial infarction [MI], stroke, arterial revascularization, hospitalization for unstable angina, or cardiovascular death) compared with placebo (HR, 0.56; 95% CI, 0.46 to 0.69; p<0.00001) [Ridker PM et al. *N Engl J Med* 2008].

Robert Glynn, PhD, Brigham and Women's Hospital, Boston, MA, presented findings from another prespecified analysis of the JUPITER data, assessing the effect of rosuvastatin on symptomatic venous thromboembolism (VTE), which occurred about as often as MI or stroke in the JUPITER study. Compared with placebo, rosuvastatin was associated with a 43% reduction (HR, 0.57; 95% CI, 0.37 to 0.86; p=0.007) in risk of VTE and no increase in bleeding [Glynn RJ et al. *N Engl J Med* 2009].

Rosuvastatin reduced the occurrence of both provoked (p=0.03) and unprovoked (p=0.09) VTE (Figure 1). Although the incidence of both pulmonary embolism and DVT was reduced, DVT alone was significantly reduced (p=0.004). The benefit of rosuvastatin was consistent across patient subgroups, based on baseline variables, while VTE reduction was independent of a prior cardiovascular event. Among patients who had VTE as the first event, there was a significant 43% reduction in risk (HR, 0.57; 95% CI, 0.37 to 0.86; p=0.007), similar to the 44% reduction in risk that was associated with rosuvastatin for the prevention of a first cardiovascular event.

Figure 1. JUPITER Venous Thromboembolism—Unprovoked versus Provoked.



When questioned regarding the likely underlying mechanisms of rosuvastatin, Dr. Glynn said he believed that the most likely candidate was an anticoagulant effect, noting that statins downregulate the blood coagulation cascade through decreased tissue factor expression, leading to reduced thrombin formation, as reported by Undas et al [Undas A et al. *Arterioscler Thromb Vasc Biol*

2005]. "Widening the treatment target to include prevention of VTE in addition to arterial thrombosis will increase the benefits of statin use," Dr. Glynn concluded.

Paul Ridker, MD, Brigham and Women's Hospital, Boston, MA, discussed results of another prespecified subanalysis that compared clinical outcomes between JUPITER trial participants according to achieved levels of LDL and hsCRP. The findings established hsCRP as a biomarker of risk for cardiovascular disease not only in people with known risk factors but also in asymptomatic individuals who previously were considered at average or even low risk for MI, stroke, or death from cardiovascular causes [Ridker PM et al. *Lancet* 2009].

In this subanalysis (87% of full cohort), the clinical outcomes of JUPITER trial participants were evaluated according to achieved levels of LDL (≥70 or <70 mg/dL) and hsCRP (≥2 or <2 mg/L).

After adjusting for baseline variables, rosuvastatin-treated subjects who achieved a reduction in LDL levels to <70 mg/dL had a 55% reduction in cardiovascular events (HR, 0.45; 95% CI, 0.34 to 0.60; p<0.0001); those who achieved an hsCRP reduction <2 mg/L had a 62% reduction in event rate (HR, 0.38; 95% CI, 0.26 to 0.56; p<0.0001), and those who achieved both a reduction of LDL <70 mg/dL and hsCRP <2 mg/L had a 65% CV event reduction (HR, 0.35; 95% CI, 0.23 to 0.54; p<0.0001). In individuals who achieved an LDL reduction of <70 mg/dL and hsCRP reduction of <1 mg/L, there was a 79% event rate reduction (HR, 0.21; 95% CI, 0.09 to 0.52; p<0.001). Similar effects were observed in analyses that were based on apolipoprotein (Apo) B or ApoB:ApoA ratio rather than on LDL.

Dr. Ridker pointed out that the impact of hsCRP reduction appears to be independent of LDL, because less than 2% of the variance in achieved hsCRP was explained by the variance in achieved LDL. This fits with previous study results (PROVE IT-TIMI 22 and A to Z trials) that have indicated that in patients with acute coronary ischemia who were treated with statin therapy, greater clinical benefits were achieved when hsCRP levels were reduced to below 1 to 2 mg/L [Ridker PM et al. *N Engl J Med* 2005; Morrow DA et al. *Circulation* 2006].

Despite these encouraging results, Dr. Ridker stressed that for patients with raised LDL or raised hsCRP, initial interventions should include dietary restrictions, exercise, and smoking cessation. However, he estimated that applying the JUPITER screening and treatment strategy to the overall US population for 5 years could prevent more than 250,000 cardiovascular disease-related events.

Patients Receiving Hemodialysis for Treatment of End-Stage Renal Disease Did Not Benefit From Statin Therapy: Results of the AURORA Trial

Rosuvastatin did not improve cardiovascular morbidity and mortality in patients who had end-stage renal disease (ESRD) and who were on hemodialysis, according to results of the large, randomized, placebo-controlled AURORA (A study to evaluate the Use of Rosuvastatin in subjects On Regular hemodialysis: an Assessment of survival and cardiovascular events; NCT00240331) trial. There was no difference between rosuvastatin 10 mg and placebo in reducing the combined endpoint of cardiovascular death, nonfatal stroke, and nonfatal myocardial infarction (MI) or any of the individual components of this endpoint when analyzed separately. The results were presented by Bengt Fellström, MD, University Hospital, Uppsala, Sweden [Fellström B et al. *New Engl J Med* 2009].

A number of studies have shown that statins lower the incidence of cardiovascular events in high-risk patients; however, it was unknown if they would have a similar effect in patients with ESRD who were on hemodialysis. A previous study with atorvastatin failed to demonstrate that statins have a statistically significant effect in reducing cardiovascular events in diabetic patients on hemodialysis with ESRD [Wanner C et al. *New Engl J Med* 2005].

Results from AURORA showed no statistically significant difference between the rosuvastatin 10 mg daily group and the placebo group in the primary endpoint of major cardiovascular event (defined as cardiovascular death, nonfatal MI, or nonfatal stroke). A major cardiovascular event occurred in 396 rosuvastatin-treated subjects and 408 subjects who received placebo (HR, 0.96; 95% CI, 0.84 to 1.11; p=0.59; Figure 1). There were no statistically significant differences in any of the secondary endpoints, including any death (p=0.51), noncardiovascular death (p=0.34), major cardiovascular event-/cause-specific death (p=0.30), atherosclerotic cardiac event (p=0.64), vascular access procedure for hemodialysis (p=0.19), and coronary or peripheral revascularization (p=0.88). Rosuvastatin achieved a 43% reduction in LDL cholesterol at 3 months, from a mean baseline level of 100 mg/dL (2.6 mmol/L), compared with a 1.9% reduction in the placebo group (p<0.001). Rosuvastatin reduced total cholesterol at 3 months by 26.6% from baseline, compared with a 0.5% reduction in the placebo group (p<0.001), and