Implications of JUPITER results for patients with normal low-density lipoprotein cholesterol and elevated C-reactive protein

Caring for patients with normal LDL-C levels

By Rene Olivares, MD, and Robert J. Chilton, DO, MPH

The results of Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) have generated tremendous discussion in the medical community about the use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) in patients with normal cholesterol levels but elevated C-reactive protein (CRP) levels. These findings were published in the November 2008 New England Journal of Medicine and were part of an associated presentation at the American Heart Association’s 2008 Scientific Sessions.

To begin our discussion, some physicians cite examples of apparently healthy patients who have low-density lipoprotein cholesterol (LDL-C) levels of approximately 105 mg per deciliter and elevated high-sensitivity CRP levels. Results of JUPITER suggest that one could reduce such a person’s cardiovascular morbidity and mortality by 50% by treating him or her with rosuvastatin calcium. However, other physicians might wonder if, in this very low-risk population, benefits of treatment would outweigh the cost of medication and possible adverse effects from exposure of the patient to lifelong drug therapy.

Physicians are aware that many patients with normal LDL-C levels can suffer myocardial infarction by following the current National Cholesterol Education Program (NCEP) guidelines, and that statin therapy may be of importance in the day-to-day care of these patients.

In JUPITER, 41% of patients with normal LDL-C levels had metabolic syndrome—a condition that is well known to increase the risk for cardiovascular events. Yet, according to the current NCEP guidelines, a patient with a normal LDL-C level does not require treatment.

This article examines implications of JUPITER trial results for such patients. First, however, we consider whether high-sensitivity CRP is only a biomarker of atherosclerosis or a causal risk factor in the pathogenesis of atherosclerosis.

Is CRP more than a biomarker?

Evidence from epidemiology studies supports the association of elevated CRP levels with increased cardiovascular events, with many risk factors involved in this association.

Although the statistical strength of this association is strong, it does not necessarily follow that high CRP levels directly cause cardiovascular disease. For example, in the Reykjavik Study by researcher John Danesh the odds ratio for coronary heart disease was 1.92 (95% confidence interval, 1.68 to 2.18) among patients with values in the top third (cutoff value, 2.0 mg per liter), as compared with the bottom third (cutoff value, 0.78 mg per liter), of base-line C-reactive protein concentrations in the control group.

In the Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) study, Wolfgang Koenig, MD, et al found that CRP was elevated in patients with low socioeconomic status (P<.04).

Levels of CRP are especially susceptible to many other confounders, such as hypertension, diabetes mellitus, body weight and lipid levels. Consequently, the physician is presented with difficult decisions when considering treatment options for the patient with elevated high-sensitivity CRP levels and normal lipid levels.

In an endeavor to answer the question of whether CRP process is only a biomarker of atherosclerosis or causally related to atherosclerosis, Jeppe Zacho, MD, et al used a Mendelian randomization approach to perform genomic evaluation (ie, genotyping) of four CRP genetic variants and two apolipoprotein E genetic variants in 50,816 subjects.

Patients with the CRP variants had elevated CRP levels, and patients with the apolipoprotein E variants had elevated lipid levels. Patients with apolipoprotein E variant genotypes also had elevated cholesterol levels and increased risk of ischemic vascular disease. By contrast, the four CRP polymorphisms were associated with increased CRP levels but not with increased risk of ischemic vascular disease.

Physicians are aware that many patients with normal LDL-C levels can suffer myocardial infarction by following the current National Cholesterol Education Program (NCEP) guidelines, and that statin therapy may be of importance in the day-to-day care of these patients.

In JUPITER, 41% of patients with normal LDL-C levels had metabolic syndrome—a condition that is well known to increase the risk for cardiovascular events. Yet, according to the current NCEP guidelines, a patient with a normal LDL-C level does not require treatment.

This article examines implications of JUPITER trial results for such patients. First, however, we consider whether high-sensitivity CRP is only a biomarker of atherosclerosis or a causal risk factor in the pathogenesis of atherosclerosis.

Is CRP more than a biomarker?

Evidence from epidemiology studies supports the association of elevated CRP levels with increased cardiovascular events, with many risk factors involved in this association.

Although the statistical strength of this association is strong, it does not necessarily follow that high CRP levels directly cause cardiovascular disease. For example, in the Reykjavik Study by researcher John Danesh the odds ratio for coronary heart disease was 1.92 (95% confidence interval, 1.68 to 2.18) among patients with values in the top third (cutoff value, 2.0 mg per liter), as compared with the bottom third (cutoff value, 0.78 mg per liter), of base-line C-reactive protein concentrations in the control group.

In the Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) study, Wolfgang Koenig, MD, et al found that CRP was elevated in patients with low socioeconomic status (P<.04).

Levels of CRP are especially susceptible to many other confounders, such as hypertension, diabetes mellitus, body weight and lipid levels. Consequently, the physician is presented with difficult decisions when considering treatment options for the patient with elevated high-sensitivity CRP levels and normal lipid levels.

In an endeavor to answer the question of whether CRP process is only a biomarker of atherosclerosis or causally related to atherosclerosis, Jeppe Zacho, MD, et al used a Mendelian randomization approach to perform genomic evaluation (ie, genotyping) of four CRP genetic variants and two apolipoprotein E genetic variants in 50,816 subjects.

Patients with the CRP variants had elevated CRP levels, and patients with the apolipoprotein E variants had elevated lipid levels. Patients with apolipoprotein E variant genotypes also had elevated cholesterol levels and increased risk of ischemic vascular disease. By contrast, the four CRP polymorphisms were associated with increased CRP levels but not with increased risk of ischemic vascular disease.

Physicians are aware that many patients with normal LDL-C levels can suffer myocardial infarction by following the current National Cholesterol Education Program (NCEP) guidelines, and that statin therapy may be of importance in the day-to-day care of these patients.

In JUPITER, 41% of patients with normal LDL-C levels had metabolic syndrome—a condition that is well known to increase the risk for cardiovascular events. Yet, according to the current NCEP guidelines, a patient with a normal LDL-C level does not require treatment.

This article examines implications of JUPITER trial results for such patients. First, however, we consider whether high-sensitivity CRP is only a biomarker of atherosclerosis or a causal risk factor in the pathogenesis of atherosclerosis.

Is CRP more than a biomarker?

Evidence from epidemiology studies supports the association of elevated CRP levels with increased cardiovascular events, with many risk factors involved in this association.

Although the statistical strength of this association is strong, it does not necessarily follow that high CRP levels directly cause cardiovascular disease. For example, in the Reykjavik Study by researcher John Danesh the odds ratio for coronary heart disease was 1.92 (95% confidence interval, 1.68 to 2.18) among patients with values in the top third (cutoff value, 2.0 mg per liter), as compared with the bottom third (cutoff value, 0.78 mg per liter), of base-line C-reactive protein concentrations in the control group.

In the Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) study, Wolfgang Koenig, MD, et al found that CRP was elevated in patients with low socioeconomic status (P<.04).

Levels of CRP are especially susceptible to many other confounders, such as hypertension, diabetes mellitus, body weight and lipid levels. Consequently, the physician is presented with difficult decisions when considering treatment options for the patient with elevated high-sensitivity CRP levels and normal lipid levels.

In an endeavor to answer the question of whether CRP process is only a biomarker of atherosclerosis or causally related to atherosclerosis, Jeppe Zacho, MD, et al used a Mendelian randomization approach to perform genomic evaluation (ie, genotyping) of four CRP genetic variants and two apolipoprotein E genetic variants in 50,816 subjects.

Patients with the CRP variants had elevated CRP levels, and patients with the apolipoprotein E variants had elevated lipid levels. Patients with apolipoprotein E variant genotypes also had elevated cholesterol levels and increased risk of ischemic vascular disease. By contrast, the four CRP polymorphisms were associated with increased CRP levels but not with increased risk of ischemic vascular disease.
To answer more definitively the question regarding treatment of patients with elevated CRP levels, a drug trial that reduces only CRP without lowering lipids is required. Certainly, the JUPITER\(^1\) results have enhanced the interest in a trial of this type. Furthermore, it is clear that genomic studies such as Dr Zacho et al\(^7\) are affecting clinical medicine.

**JUPITER—to treat or not to treat?**

JUPITER\(^1\) was a large primary prevention trial that enrolled patients who had elevated high-sensitivity CRP levels but did not have hyperlipidemia. In this trial, 17,802 apparently healthy men and women with LDL-C levels of less than 130 mg per deciliter and high-sensitivity CRP levels of more than 2.0 mg per liter were randomized to receive either rosuvastatin (20 mg daily) or placebo.

The primary outcome was the occurrence of a first major cardiovascular event, which was defined as nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, an arterial revascularization procedure, or confirmed death from cardiovascular causes.

JUPITER\(^1\) was terminated early, after 142 first major cardiovascular events had occurred in the rosuvastatin group, compared with 251 such events in the placebo group [hazard ratio, 0.56; 95% confidence interval (CI), 0.46-0.69; \(P<.001\)]. The median follow-up time was 1.9 years and the maximum follow-up time was five years.

During JUPITER\(^1\), the primary endpoint event rate was very low in both groups—1.5% in the treatment arm and 2.8% in the control arm. Baseline characteristics of enrolled patients are of note, with 41% of the patients having metabolic syndrome. The patients’ baseline median glucose level was 94 mg per deciliter and the baseline median body mass index (BMI) was 28.

Results of the trial showed that rosuvastatin reduced the median CRP level by 37% and the median LDL-C level by 50%. In addition, the level of high-density lipoprotein cholesterol increased from a median of 49 mg per deciliter at baseline to 50 mg per deciliter at 48 months.

A review of the major cardiovascular event reductions in JUPITER\(^1\) yields important clinical implications. Patients in the placebo arm had a very low cardiovascular event rate, of 1.36% per year, for myocardial infarction, stroke, revascularization, or hospitalization for unstable angina or death.

Current NCEP guidelines\(^3\) do not recommend treatment for patients with such a low cardiovascular risk. Patients treated with rosuvastatin in JUPITER\(^1\) had a cardiovascular event rate of 0.77% per year, with a relative risk reduction of 44% compared with patients in the placebo arm [hazard ratio, 0.56; 95% CI, 0.46-0.69; \(P<.001\)]. Moreover, treatment of patients in this low-risk group resulted in a nearly 50% reduction in cardiovascular mortality and morbidity.

Special subgroups in JUPITER\(^1\) are worthy of mention. The results in 6,801 women who were treated with rosuvastatin were impressive, with a reduction in the primary endpoint of 46%. Low-risk patients treated with rosuvastatin who had a Framingham Risk Score less than 10%, a BMI less than 25, and who were nonsmokers without metabolic syndrome had similar relative reductions in the hazard ratio as did the higher risk groups.

One might have expected that patients with metabolic syndrome and other high-risk conditions would have received greater benefit in cardiovascular event reduction from rosuvastatin than patients with low-risk conditions. Nevertheless, in patients with no major risk factor other than increased age and elevated high-sensitivity CRP levels, JUPITER\(^1\) results showed that the benefit of rosuvastatin use was similar to that in higher-risk patients [hazard ratio, 0.63; 95% CI, 0.44-0.92; \(P=.01\)]. Thus, it would appear that high-risk and low-risk patients, women and possibly other subgroups all benefit from treatment with rosuvastatin.

The addition of rosuvastatin substantially reduced cardiovascular events in JUPITER\(^1\) patients.

Mechanisms frequently suggested for such cardiovascular event reduction are the lowering of lipid levels and high-sensitivity CRP levels. However, it should be noted that there are clearly vascular effects beyond lipid level changes, and that the lowering of high-sensitivity CRP levels may have important benefits yet to be discovered.

(Continued on the following page)
During JUPITER, there was an unexpected increase in physician-reported diabetes mellitus with use of rosuvastatin (3% in statin group vs 2.4% in placebo group, P<.02). The exact explanation for this increase continues to be evaluated. Further studies will be required to fully address this concern.

The occurrence of adverse events was remarkably low in JUPITER, with similar numbers of adverse events in the rosuvastatin and placebo groups (1,352 and 1,377, respectively; P=.60). Nineteen myopathic events were reported, including 10 patients who received rosuvastatin and nine patients who received placebo (P=.82).

These results are certainly reassuring for the clinician—even with the higher dose (20 mg) of rosuvastatin and with the clinical consideration for earlier primary prevention treatment in patients with elevated high-sensitivity CRP levels and no hyperlipidemia. Concerns regarding lifelong (ie, >20-40 years) safety of statins should be added to treatment. Our personal opinion regarding treatment rests on evaluation of a patient’s 10-year risk for a cardiovascular event.

Treatment of low-risk patients should continue with lifestyle modification and exercise. Treatment of patients at intermediate risk (10%-15% cardiovascular risk at 10 years) should start with lifestyle modification and exercise, leading to incorporation of guideline targets for known risk factors (ie, global risk reduction).

Patients with metabolic syndrome are at very high risk, and current clinical judgment would base treatment on correcting all risk factors to goal. However, it is important to remember that the most important treatment goal is weight loss (if the patient has an elevated BMI), and achieving this goal, unfortunately, is typically the toughest pill for patients to swallow.

References

Rene Olivares, MD, is associate professor of medicine and director of the Coronary Care Unit at the University of Texas Health Science Center/Audie Murphy Veterans Affairs Medical Center, Fort Worth, Texas. Dr Olivares is a Fellow of the American College of Cardiology.

Robert J. Chilton, DO, MPH, is professor of medicine and director of the cardiac catheterization laboratory at the University of North Texas Health Science Center/Audie Murphy Veterans Affairs Medical Center, Fort Worth, Texas. Dr Chilton is a Fellow of the American College of Cardiology. He can be reached at Chilton@uthsc.edu.