



July 2007

Dear Colleagues:

Greetings. Welcome to the inaugural issue of the *Clinical Insights® in Lipid Management* newsletter, a continuing medical education (CME)-certified activity under the auspices of the Committee on Cardiovascular and Metabolic Diseases™ (CCMD™) initiative. Sponsored by Professional Postgraduate Services®, the CCMD is a longstanding, multifaceted, multigrantor-supported educational initiative focusing on the management of cardiovascular and metabolic diseases to modify or reduce global cardiovascular risk.

Every month, *Clinical Insights® in Lipid Management* will present a series of reviews of current clinical literature regarding the diagnosis and management of dyslipidemia. Further, each issue will include a commentary from a CCMD Education Council or Faculty member, addressing the clinical significance of the “lead” article. The newsletter provides an important evidence-based platform to examine clinical-trial results, explore new science in the pathophysiology of dyslipidemia and its impact on overall health and medical comorbidities, and assess the reasons why patients are not achieving their treatment goals. Our ultimate objective is to help you, the practicing clinician, improve outcomes for your patients.

Each newsletter will be available as a PDF on the CCMD award-winning website, www.CCMDweb.org, and as a podcast on both www.CCMDweb.org and iTunes. Each issue will be certified for *AMA PRA Category 1 Credit™*.

On behalf of the entire CCMD, we welcome you to this educational activity and look forward to your participation every month. Please do let us know your thoughts; your input is important in helping us design high-quality education programs.

Sincerely,

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Applicants will receive a certificate of participation from PPS by return mail within 6 to 8 weeks of the date of receipt of the completed evaluation form. Online applicants will automatically receive their CME credit certificate upon completion of the online post-test and evaluation form.

Target Audience

This educational activity is designed for primary care physicians, endocrinologists, cardiologists, internists, and other healthcare professionals involved in the diagnosis and management of dyslipidemia and its comorbidities.

Learning Objectives

With information from the latest evidence-based studies, participants should be able to:

- Detail the anti-inflammatory effects of combination lipid-lowering therapies incorporating different mechanisms of action
- Recognize the worsened prognosis for patients with preexisting atherosclerosis who have the metabolic syndrome
- Identify the gap in treatment for patients at presumptive high cardiovascular risk (ie, in chest pain units)

Accreditation

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Grantor

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Off-Label Disclosure

Some of the drug treatments discussed in this issue may note uses not approved by the Food and Drug Administration. Articles containing such uses will be noted at the end of the article.

Additional PPS Staff Disclosures

Natasha K. McIntyre, Program Assistant; Wade'ah Terry, CME Program Manager; and Caroline Tredway, Editorial Director, have all indicated no relevant financial relationships.

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JOHN C. LAROSA, MD^a, CO-EDITOR, COMMENTATOR, AND REVIEWER; MARK A. PALANGIO^b, WRITER

Ezetimibe + Simvastatin Produces Greater CRP Reductions than Simvastatin, But Similar to Atorvastatin

Earlier investigations have demonstrated that combination therapy with ezetimibe plus a statin results in significant reductions in C-reactive protein (CRP) levels, in addition to lowering low-density lipoprotein cholesterol (LDL-C) levels, relative to statin monotherapy. Ezetimibe is a novel anti-hyperlipidemic medication that inhibits intestinal absorption of cholesterol from dietary and biliary sources, thereby lowering serum LDL-C. In a large cohort of patients with primary hypercholesterolemia, Pearson and colleagues compared the anti-inflammatory and lipid-modifying effects of ezetimibe/simvastatin combination therapy with those of simvastatin and atorvastatin monotherapy across the marketed doses.

This analysis combined data from three identical, prospective 12-week trials (pooled simvastatin factorial studies) in which patients were randomized to receive placebo; ezetimibe 10 mg; ezetimibe 10 mg added to simvastatin 10 mg, 20 mg, 40 mg, or 80 mg; or simvastatin 10 mg, 20 mg, 40 mg, or 80 mg. Additionally, to compare combination ezetimibe/simvastatin with atorvastatin, data were analyzed from a phase III double-blind, active-controlled, 6-week study (atorvastatin factorial study) in which patients were randomized equally to receive ezetimibe/simvastatin 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, or 10 mg/80 mg or atorvastatin 10 mg, 20 mg, 40 mg, or 80 mg.

Paired baseline and post-treatment CRP values were available for 2,541 patients in the three pooled simvastatin factorial studies and 1,832 patients from the atorvastatin factorial study.

Averaged across doses, ezetimibe/simvastatin elicited significantly greater reductions in LDL-C compared with simvastatin alone (-52.5% vs -38.0%, respectively; $P < 0.001$) after 12 weeks.

Likewise, averaged across doses, ezetimibe/

simvastatin produced significantly greater reductions in LDL-C compared with atorvastatin alone (-53.4% vs -45.3%, respectively; $P < 0.001$).

Averaged across doses, ezetimibe/simvastatin produced significantly greater geometric mean reductions in CRP levels compared with simvastatin alone (-31.0% vs -14.3%, respectively; $P < 0.001$), resulting in an incremental reduction of 16.7% (95% confidence interval [CI], 11.7%–21.7%) favoring combination therapy. Moreover, significantly greater geometric mean percentage reductions in CRP were achieved with ezetimibe/simvastatin versus each corresponding dose of simvastatin monotherapy ($P < 0.01$ for each comparison). However, there were no significant differences in geometric mean percentage reductions in CRP between ezetimibe/simvastatin and

atorvastatin when averaged across doses (-25.1% vs -24.8%, respectively) and at each milligram-equivalent statin dose comparison.

In this analysis, ezetimibe/simvastatin produced significantly greater CRP reductions compared with simvastatin monotherapy and similar CRP reductions compared with atorvastatin monotherapy. The study investigators speculated that ezetimibe might potentiate the effects of statins on hepatic CRP production after a threshold of LDL-C reduction is reached ($\geq 30\%$ reduction). Yet, the investigators also pointed out that the CRP reduction observed here might not necessarily correlate with a reduction in arterial inflammation or cardiovascular disease risk. Consequently, further trials with clinical endpoints are required.

Pearson T, Ballantyne C, Sisk C, et al. Comparison of effects of ezetimibe/simvastatin versus simvastatin versus atorvastatin in reducing C-reactive protein and low-density lipoprotein cholesterol levels. *Am J Cardiol.* 2007;99:1706-1713.

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COMMENTARY

JOHN C. LaROSA, MD, President of SUNY Downstate Medical Center, Brooklyn, New York. Education Council Member, Committee on Cardiovascular and Metabolic Diseases™ (CCMD™)

This article presents a direct comparison of atorvastatin (10 mg/d–80 mg/d), simvastatin (10 mg/d–80 mg/d), and a combination of simvastatin (10 mg/d–80 mg/d) and ezetimibe (10 mg/d).

LDL-C lowering with high-dose atorvastatin is somewhat better than with high-dose simvastatin (-53% vs -46%). The greatest LDL-C response, however, is with the simvastatin 80 mg/ezetimibe 10 mg combination (-60%). The addition of ezetimibe at all dose levels of simvastatin virtually doubles the decline in C-reactive protein (CRP) levels compared with simvastatin alone.

Since the CRP lowering seen with statin therapy has been postulated to be evidence of the statin “anti-inflammatory” effects, it is unsettling that ezetimibe, a drug that has little effect on CRP when given alone, has a strong CRP lowering when combined with simvastatin. These results strongly imply either that there is a not yet identified, and generalized, effect of ezetimibe on statins, or that the assumption that CRP levels are evidence of anti-inflammatory activity should be re-examined.

The authors hypothesize that the ezetimibe CRP effect, because of ezetimibe’s enterohepatic circulation, may be the result of inhibition of hepatic CRP synthesis rather than suppression of inflammation. That is purely conjectural, however. At the least, these results should dampen enthusiasm for assuming that changes in circulatory CRP levels reflect changes in intravascular inflammatory activity. What, if anything, CRP changes do signify remains uncertain.

Post-Test Question 1

Based on the results of this recent study, which of the following statements is *false*?

- Ezetimibe/simvastatin produced significantly greater reductions in LDL-C level compared with simvastatin alone
- Ezetimibe/simvastatin produced significantly greater reductions in LDL-C level compared with atorvastatin alone
- Ezetimibe/simvastatin produced significantly greater reductions in CRP levels compared with simvastatin alone
- Ezetimibe/simvastatin produced significantly greater reductions in CRP levels compared with atorvastatin alone

Metabolic Syndrome Worsens Prognosis in Patients With Preexisting Atherosclerosis

Although it is well recognized that metabolic syndrome (MetS) increases the risk of cardiovascular atherosclerosis, little is known about its impact on cardiovascular prognosis in the setting of atherosclerotic burden. As such, Espinola-Klein and associates examined the relationship between MetS and long-term prognosis among patients with atherosclerotic burden.

This study included 811 Caucasian patients (mean age, 63 years) with coronary heart disease (CHD) who were admitted to the University Hospital of Mainz, Germany, for diagnostic heart catheterization between November 1996 and July 1998. Carotid and leg arteries were examined using sonographic methods. The rates of cardiovascular events (myocardial infarction, stroke, and cardiovascular-related death) were compared between patients with low atherosclerotic burden (ie, CHD only) and those with high atherosclerotic burden (ie, CHD and peripheral atherosclerosis).

In this study group, 428 patients (52.8%) had low atherosclerotic burden whereas 383 (47.2%) had high atherosclerotic burden. MetS was detected in 349 patients (43.0%). The median follow-up was 6.7 years.

Cardiovascular event rates were significantly higher in patients with MetS compared with those without MetS (27.9% vs 17.0%, respectively; $P < 0.0001$). Moreover, MetS was identified as an independent predictor for cardiovascular events

(hazard ratio [HR], 1.7; 95% confidence interval [CI], 1.3–2.3; $P < 0.0001$, adjusted).

Among patients with low atherosclerotic burden, the cardiovascular event rate was significantly higher in the presence of MetS than in the absence of MetS (21.2% vs 12.9%; $P = 0.02$). The disparity in cardiovascular event rates between patients with and without MetS was even more prominent among patients with high atherosclerotic burden (34.3% vs 26.5%; $P = 0.01$). MetS was identified as an independent predictor for cardiovascular events in patients with high atherosclerotic burden in particular (HR, 1.8, 95% CI, 1.2–2.6; $P = 0.005$, adjusted).

These results indicate that patients with MetS and preexisting atherosclerosis are at a substantially higher risk of cardiovascular events over the long-term than those without MetS. Furthermore, MetS considerably worsens the long-term prognosis of patients with both low and high atherosclerotic burden, but does so to a greater extent among those with high atherosclerotic burden. Hence, the study investigators suggest that patients with high atherosclerotic burden and MetS should be considered a high-risk population and treated appropriately.

Espinola-Klein C, Rupprecht HJ, Bickel C, et al. Impact of metabolic syndrome on atherosclerotic burden and cardiovascular prognosis. *Am J Cardiol.* 2007;99:1623-1628.

Post-Test Question 2

In this study, MetS was found to considerably worsen the long-term cardiovascular prognosis of patients with which of the following?

- Low atherosclerotic burden (ie, CHD only)
- High atherosclerotic burden (ie, CHD and peripheral atherosclerosis)
- Both low and high atherosclerotic burden
- None of the above

Poor Screening and Treatment of Hypercholesterolemia in a Chest Pain Observation Unit

Recently, Gillespie et al evaluated the prevalence of hypercholesterolemia and the opportunity to initiate statin therapy among subjects admitted to a chest pain observation unit (CPOU). This retrospective cross-sectional analysis involved 574 patients who were deemed low-risk for acute coronary syndrome and who were admitted to the CPOU at the University of North Carolina at Chapel Hill between September 2002 and September 2003.

For all patients, 10-year Framingham risk scores were retrospectively calculated according to the National Cholesterol Education Program and Adult Treatment Panel III 2001 (NCEP ATP III 2001) recommendations. Patients were subsequently stratified according to recommendations for initiation of a lipid-lowering medication and whether they received lipid-lowering drug therapy at discharge.

Of 574 subjects, 50 were excluded because of previously established coronary heart disease or because they were already taking a statin medication on presentation, 23 were excluded because of missing data, and 80 (16%) were excluded because low-density lipoprotein cholesterol (LDL-C) was not measured on admission.

In the group of 421 remaining subjects, the mean age was 47 years, 40% were men, 57% were white, 31% had hypertension, 27% were current smokers, and 6% had diabetes. Based on Framingham risk scores, 47% (n=199) were classified as low risk (<2 risk factors), 32% (n=134) as moderate risk (≥ 2 risk factors and <10% risk), 11% (n=48) as moderate-high risk (10%–20% risk), and 10%

(n=40) as high risk (>20% risk). In this cohort, 34% (n=134) of subjects had multiple (≥ 2) risk factors and a 10-year risk <10%, 11% (n=48) had multiple risk factors and a 10-year risk of 10% to 20%, and 10% (n=40) had multiple risk factors and a 10-year risk of $\geq 20\%$.

In this study, 23% of subjects (n=96) had hypercholesterolemia and 52% (n=50) met the NCEP ATP III 2001 recommendations for initiation of lipid-lowering medication. Remarkably, only 6% of patients with an indication for treatment (n=3) were prescribed a lipid-lowering medication on discharge, leaving 94% (n=47) untreated for their hypercholesterolemia.

This study revealed that patients admitted to a CPOU have a high prevalence of hypercholesterolemia, and consequently, are at increased risk for cardiovascular events. Additionally, 16% of subjects were not screened during admission for hypercholesterolemia with a fasting lipid panel. Most notably, 94% of patients with hypercholesterolemia who met the indication for treatment did not receive a lipid-lowering medication on discharge. The study investigators suggested that, in addition to their primary role, CPOUs should concentrate on the screening and treatment of hypercholesterolemia.

Gillespie MJ, Davis CJ, Lambert ND, et al. Measuring and treating serum lipids in patients in a chest pain observation unit. *Am J Cardiol.* 2007;99:1718-1720.

Post-Test Question 3

This study revealed that:

- Patients admitted to a CPOU have a high prevalence of hypercholesterolemia
- Not all patients admitted to a CPOU are screened for hypercholesterolemia
- Most patients with hypercholesterolemia who met the indication for treatment do not receive a lipid-lowering medication on discharge
- All of the above

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