

**RELEASE DATE:** May 12, 2008  
**VALID THROUGH:** November 12, 2008

**SPONSOR**

This educational activity is conducted as a part of the Committee on Cardiovascular and Metabolic Diseases<sup>™</sup> (CCMD<sup>™</sup>), sponsored by Professional Postgraduate Services<sup>®</sup> (PPS), Secaucus, NJ.

Clinicians who wish to receive continuing medical education (CME) credit for this educational activity should read the current issue and complete the posttest and evaluation form on our website, [www.CCMDweb.org](http://www.CCMDweb.org)

You will automatically receive your CME credit certificate upon completion of the online posttest 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:
- Describe the effects of ezetimibe plus simvastatin on atherosclerotic progression in patients with familial hypercholesterolemia
  - Recognize the association between lipoprotein(a) levels and future coronary heart disease (CHD) risk
  - Delineate the relationships of plasma HDL cholesterol levels, HDL particle size, and apolipoprotein A-I with CHD risk

**ACCREDITATION**

Professional Postgraduate Services<sup>®</sup> is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Professional Postgraduate Services<sup>®</sup> designates this educational activity for a maximum of 0.50 AMA PRA Category 1 Credit<sup>™</sup>. Physicians should only claim credit commensurate with the extent of their participation in the activity.

*Clinical Insights*<sup>®</sup> in *Lipid Management* has been reviewed and is acceptable for up to 6 Prescribed credits by the American Academy of Family Physicians (AAFP). AAFP accreditation begins 07/01/07 and the term of AAFP approval is for 1 year from this date. This issue is approved for 0.50 Prescribed credit, which may be claimed for 1 year from the date of this issue.

**GRANTOR**

The CCMD<sup>™</sup> is supported by educational grants from Pfizer Inc, AstraZeneca, Reliant Pharmaceuticals, Inc., Abbott Laboratories, and Takeda Pharmaceuticals North America, Inc.

This activity is supported by an educational grant from Takeda Pharmaceuticals North America, Inc.

**PPS STAFF DISCLOSURES**

Danielle Gabriel, Senior Managing Editor; Al Tauriello, Associate Editor; Sydel Cohen, Program Manager; Elizabeth Ward, CME Director; and Wade'ah Terry, CME Program Manager, have all indicated no relevant financial relationships.

**OFF-LABEL DISCLOSURE**

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

Copyright © 2008 Professional Postgraduate Services<sup>®</sup>. All rights reserved.

PETER LIBBY, MD,<sup>a</sup> CO-EDITOR, REVIEWER, AND COMMENTATOR;  
MARK PALANGIO,<sup>b</sup> WRITER

## Lack of Reduction in Atherosclerotic Progression With Addition of Ezetimibe to Simvastatin in Familial Hypercholesterolemia: Results of the ENHANCE Trial

**L**ow-density lipoprotein cholesterol (LDL-C) is the main therapeutic target in the prevention of cardiovascular disease (CVD). Indeed, more aggressive lowering of LDL-C levels with statin therapy has produced greater reductions in cardiovascular event rates. Ezetimibe, a cholesterol-absorption inhibitor, has been shown to further reduce LDL-C levels when added to statin therapy. However, the effects of this combination on atherosclerotic progression is unknown. Kastelein and colleagues assessed whether simvastatin plus ezetimibe could reduce carotid intima-media thickness (CIMT) progression better than simvastatin alone among patients with familial hypercholesterolemia (FH), a condition linked to premature CVD.

The Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial was a double-blind, randomized, 24-month study that compared the effects of simvastatin 80 mg qd (the highest recommended dose; n=363) with those of simvastatin 80 mg qd plus ezetimibe 10 mg qd (n=357; combined-therapy group) in a cohort with FH. The primary outcome was change from baseline in ultrasonographic measurement of the mean CIMT (the average of the means of the far-wall IMT of the right and left common carotid arteries, carotid bulbs, and internal carotid arteries).

The average age of participants was 46 years, 51% were men, and 81% had been previously treated with statin therapy. After 24 months, mean ( $\pm$  standard deviation) LDL-C levels decreased from 317.8 $\pm$ 66.1 mg/dL to 192.7 $\pm$ 60.3 mg/dL in the simvastatin-

only group and from 319.0 $\pm$ 65.0 mg/dL to 141.3 $\pm$ 52.6 mg/dL in the combination-therapy group, a significant between-group difference of 16.5% ( $P<0.01$ ). Similarly, reductions in triglycerides and C-reactive protein (CRP) were significantly greater in the combination-therapy group than in the simvastatin-only group ( $P<0.01$  for both comparisons), with between-group differences of 6.6% and 25.7%, respectively.

In contrast, there was no significant difference in the primary outcome in the mean ( $\pm$  standard error) change of CIMT between the simvastatin-only group (0.0058 $\pm$ 0.0037 mm) and the combination-therapy group (0.0111 $\pm$ 0.0038 mm;  $P=0.29$ ). Further, secondary outcomes did not differ significantly between the two groups. Mean CIMT regression was noted in 44.4% of patients in the simvastatin-only group and in 45.3% of patients in the combination-therapy group ( $P=0.92$ ). New plaque formation (IMT >1.3 mm) was observed in 2.8% of

patients in the simvastatin-only group and in 4.7% of patients in the combination-therapy group ( $P=0.20$ ). There was also no significant difference in mean maximum CIMT change ( $P=0.27$ ); and mean measures of the IMT of the common carotid artery ( $P=0.93$ ), carotid bulb ( $P=0.37$ ), internal carotid artery ( $P=0.21$ ), and femoral artery ( $P=0.16$ ) between both groups; the average of the mean values for IMT in the carotid and femoral arteries ( $P=0.15$ ) was also not significantly different between groups. Treatment-related adverse events (AEs) and discontinuations due to AEs were similar in both groups.

*Continued*

*“Appreciation of the clinical implications of the ENHANCE trial requires understanding the crucial difference between biomarkers and clinical endpoints.”*

*Peter Libby, MD*

*(See full commentary on page 2.)*

<sup>a</sup> Dr Libby has indicated financial relationships as noted: consultant for AstraZeneca, GlaxoSmithKline, Schering-Plough, Merck & Co., Inc., Kowa Pharmaceutical Company Ltd., Novartis AG, and Pfizer Inc.

<sup>b</sup> Mr Palangio is a medical writer at Professional Postgraduate Services<sup>®</sup>. He has indicated no relevant financial relationships.

*Continued*

### **Lack of Reduction in Atherosclerotic Progression With Addition of Ezetimibe to Simvastatin in Familial Hypercholesterolemia: Results of the ENHANCE Trial**

The ENHANCE trial showed that the addition of ezetimibe to simvastatin among patients with FH did not decrease the rate of CIMT progression, despite significant incremental reductions in LDL-C and CRP levels. The authors acknowledged that the cause of this unexpected outcome is unknown but proposed three possible

explanations: a lack of vascular benefit with ezetimibe despite reduced LDL-C levels, failure of CIMT to reflect accurately atherosclerotic plaque burden, and the possibility that the study population had baseline CIMT levels too low to allow detection of a differential therapeutic response.

Kastelein JJ, Akdim F, Stroes ES, et al. Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N Engl J Med.* 2008;358(14):1431-1443.

## **NEW!**

CME-certified case study authored by CCMD Faculty Member Neil J. Stone, MD, focusing on a multifactorial approach to lipid lowering in the high-risk patient.

<http://www.CCMDweb.org>

### **Commentary**

**PETER LIBBY, MD**, Mallinckrodt Professor of Medicine, Harvard Medical School; Chief, Cardiovascular Division, Brigham and Women's Hospital, Boston, Massachusetts. Education Council Member, Committee on Cardiovascular and Metabolic Diseases™ (CCMD™).

The ENHANCE trial studied 720 patients with FH randomized to simvastatin alone or with the cholesterol-absorption inhibitor, ezetimibe. The study monitored CIMT by ultrasound. Despite a significant drop in LDL-C and in CRP in the double-treated group, CIMT was the same in both groups after 2 years.

Several large studies have shown that a single measurement of the biomarker CIMT correlates well with future cardiovascular events. Some previous studies show that a change in this biomarker over time may correlate with clinical benefit. Appreciation of the clinical implications of the ENHANCE trial requires understanding the crucial difference between biomarkers and clinical endpoints. Decades of accumulated evidence support LDL-C as a useful but not infallible biomarker of risk. Lifestyle measure should always be the first step to managing atherosclerosis risk, but many of our patients also require drug therapy to achieve mandated LDL-C goals. Overwhelming evidence shows that statin treatment in accord with guidelines can reduce cardiovascular events. Ezetimibe in addition to a statin may help LDL-C goals, but we need to await the results of clinical endpoint trials such as the IMPROVED Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) to ascertain that LDL-C lowering produced by this cholesterol-absorption inhibitor will lower cardiovascular risk.

The ENHANCE results in no way render cholesterol control invalid. We should not let a small trial that measured a relatively weak biomarker of benefit derail the decades of discoveries supporting LDL-C as a strong biomarker and a generally valid target of therapy.

## **Lipoprotein(a) Levels Are Continuously Associated With Future CHD Risk: Large-Scale Prospective Data**

**L**ipoprotein(a) (Lp[a]) is a low-density lipoprotein-like particle that is synthesized by the liver and contains an apolipoprotein B molecule covalently linked to a very large glycoprotein known as apolipoprotein(a). Numerous epidemiologic studies have evaluated the association between circulating Lp(a) levels and cardiovascular disease. Bennet and associates recently reported new primary data on the largest single study of Lp(a) concentrations and coronary heart disease (CHD) completed thus far.

This study measured Lp(a) levels in samples obtained at baseline from 2,047 patients who had first-ever nonfatal myocardial infarction or who died from CHD during the study and from 3,921 control participants in the Reykjavik Study

(n=18,569), as well as in paired samples obtained 12 years apart from 372 participants to quantify within-person fluctuations.

Predictably, levels of established cardiovascular risk factors at baseline were higher in patients with CHD than in controls. Further, baseline Lp(a) levels were higher in patients with CHD than in controls. However, there were no significant correlations between baseline Lp(a) levels and various cardiovascular risk factors, such as age, sex, total cholesterol (TC), and blood pressure (BP). In the 372 participants with paired measurements at baseline and 12 years later, Lp(a) values were highly consistent from decade to decade, with a regression dilution ratio (calculated on the log

*Continued*

Continued

### **Lipoprotein(a) Levels Are Continuously Associated With Future CHD Risk: Large-Scale Prospective Data**

scale) of 0.92 (95% confidence interval [CI], 0.85–0.99).

In a comparison of participants with baseline Lp(a) values in the top third versus bottom third, the odds ratio (OR) for CHD was unaltered after adjustment for age, sex, smoking status, BP, TC level, triglycerides, diabetes, and body mass index (OR, 1.60; 95% CI, 1.38–1.85). ORs for CHD increased progressively with increasing Lp(a) levels ( $P < 0.001$ , test for linear trend) and did not vary with several individual- or study-level characteristics.

These results revealed a continuous association between Lp(a) levels and the risk of future CHD that was independent of the effect of several established cardiovascular risk factors. Moreover, Lp(a) levels were highly stable within individuals across many years. The study investigators underscored the need for further investigation of the possible role of Lp(a) levels in CHD prevention, as well as the need for further assessment of strategies that modify Lp(a) levels.

Bennet A, Di Angelantonio E, Erqou S, et al. Lipoprotein(a) levels and risk of future coronary heart disease: large-scale prospective data. *Arch Intern Med.* 2008;168(6):598-608.

## **COMING SOON!**

A CME-certified interactive case study from CCMD Faculty Member James M. McKenney, MD, exploring the assessment and management of a primary-prevention patient with atherogenic dyslipidemia.

<http://CCMDweb.org>

## **Very High Levels of HDL-C and Very Large HDL Particle Size Are Associated With Increased CV Risk**

High levels of high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A-I (apo A-I), the main protein constituent of HDL particles, are inversely related to the risk of coronary artery disease (CAD). Yet, emerging data indicate that this relationship may not be true for very high HDL-C levels, especially with a preponderance of large HDL particles.

Recently, van der Steeg et al examined the relationships of HDL-C levels, HDL particle size, and apo A-I with CAD risk in a post hoc analysis of two prospective studies: the Incremental Decrease in End Points through Aggressive Lipid Lowering (IDEAL) trial and the European Prospective Investigation into Cancer (EPIC)-Norfolk study. IDEAL (n=8,888) compared the efficacy of high-dose statin therapy (atorvastatin 80 mg qd) to that of usual-dose statin therapy (simvastatin 20 mg qd) for the secondary prevention of cardiovascular events over a mean follow-up of 4.8 years. EPIC-Norfolk included apparently healthy individuals who did (cases; n=858) or did not (control patients; n=1,491) develop CAD during follow-up. HDL-C and apo A-I levels were available from both studies; nuclear magnetic resonance spectroscopy-determined HDL particle sizes were available only from EPIC-Norfolk. For this analysis, the occurrence of a major cardiac event was the outcome variable.

In the IDEAL trial, higher HDL-C levels were a significant major cardiac event risk factor following adjustment for age, gender, smoking, apo A-I level, and apolipoprotein B (apo B) level (relative risk [RR], 1.21; 95% confidence interval [CI], 1.01–1.46;  $P = 0.04$ ). In EPIC-Norfolk, a

similar association was observed for high HDL particle size (RR, 1.23; 95% CI, 1.07–1.42;  $P = 0.005$ ). Increased risk estimates were especially apparent in the highest categories of the distributions. In contrast, following adjustments for HDL-C and apo B levels, there was a significant negative relationship between apo A-I level and the occurrence of a major cardiac event in IDEAL (RR, 0.74; 95% CI, 0.61–0.90;  $P = 0.002$ ) and EPIC-Norfolk (RR, 0.74; 95% CI, 0.62–0.88;  $P = 0.001$ ).

Such findings suggest that a very high HDL-C level and very large HDL particle sizes are associated with increased CAD risk when levels of apo A-I and apo B remain unaffected, whereas a high apo A-I level is not a significant risk factor for major coronary events. According to the

study investigators, these results have important clinical implications, particularly with regard to assessment and treatment of CAD risk. They speculated that interventions that raise HDL-C levels without affecting apo A-I levels may not confer cardiovascular benefits and, when very high HDL-C levels are achieved, may even be detrimental.

*“These results have important clinical implications, particularly with regard to assessment and treatment of CAD risk.”*

van der Steeg WA, Holme I, Boekholdt SM, et al. High-density lipoprotein cholesterol, high-density lipoprotein particle size, and apolipoprotein A-I: significance for cardiovascular risk: the IDEAL and EPIC-Norfolk studies. *J Am Coll Cardiol.* 2008;51(6):634-642.