Journal of Clinical Lipidology (2008) 2, 313–317

Journal of Clinical Lipidology

Editorial Article

A Commentary on the implications of the ENHANCE (Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression) Trial: Should ezetimibe move to the "Back of the Line" as a therapy for dyslipidemia?

Peter P. Toth, MD, PhD,* Kevin C. Maki, PhD

Sterling Rock Falls Clinic, 101 East Miller Road, Sterling, IL 61081, USA (Dr. Toth); and Provident Clinical Research, Glen Ellyn, IL, USA (Dr. Maki)

In this commentary, the controversies surrounding the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial are evaluated in the context of other carotid intima-media thickness (CIMT) based clinical trials.

At the 2008 American College of Cardiology meeting, results from the ENHANCE trial were released, producing a firestorm of controversy among scientists and clinicians.[1–3] In the ENHANCE trial,[4] 720 patients with heterozygous familial hypercholesterolemia were randomly assigned to receive 80 mg/day of simvastatin plus either ezetimibe 10 mg/day or a placebo for two years. The primary outcome variable was the change from baseline in a composite measure of the CIMT, a surrogate marker for progression of atherosclerosis. Despite significantly lower levels of low-density lipoprotein cholesterol (LDL-C; 141 vs. 193 mg/dL), apolipoprotein B (ApoB; 135 vs. 169 mg/dL), triglycerides (108 vs. 120 mg/dL), and C-reactive protein (CRP; 0.9 vs. 1.2 mg/L) during treatment ($P \leq 0.01$ for all), the group receiving ezetimibe showed a mean change in CIMT (0.011 mm) that was no different ($P = 0.29$) from that in the group receiving placebo (0.0058 mm) (Fig. 1).

Should the ENHANCE results change clinical practice?

The panel invited to discuss the clinical implications of the ENHANCE trial at the American College of Cardiology meeting, as well as the two editorials in the *New England Journal of Medicine* that accompanied the ENHANCE paper,[1,2] recommended that, as a result of the failure to show a benefit of adding ezetimibe to simvastatin in the ENHANCE trial, ezetimibe should be reserved for use in patients who cannot tolerate other drug classes or who cannot achieve their treatment targets with statins plus niacin, fibrates, or bile acid sequestrants.

At the American College of Cardiology meeting, there was no meaningful scientific debate about possible alternative explanations for the unexpected results. Many in attendance were surprised at the negativity of the panel based on a single surrogate endpoint trial and pondered the role that politics may have played in selection of the panel members. Press coverage was heavily weighted toward the view that the ENHANCE results raise significant doubts about the usefulness of ezetimibe and many reports suggested possible harm to those taking the drug, drawing analogies to other drugs for which this has been the case, such as rofecoxib and torcetrapib. Some stories in the popular press even called into question the entire "LDL hypothesis," resulting in considerable confusion among patients, some of whom discontinued their lipid therapy. Physicians also be-

* Corresponding author.
E-mail address: peter.toth@srfc.com
Submitted May 27, 2008. Accepted for publication June 16, 2008.

1933-2874/$ -see front matter
doi:10.1016/j.jacl.2008.06.011

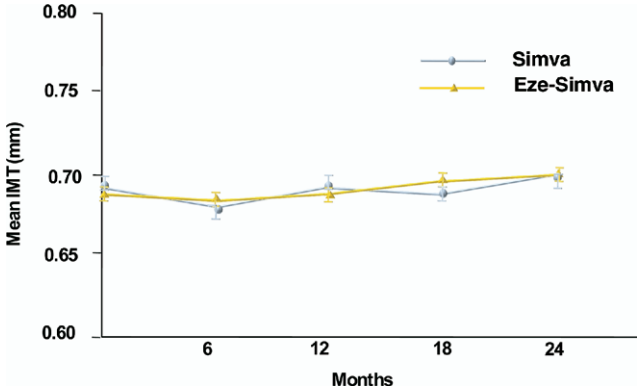

Figure 1 Mean (± SEM) values for carotid intima-media thickness in the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial.[4] *Circles* represent values for subjects who received 80 mg simvastatin (Simva) and *triangles* represent values for subjects who received simvastatin 80 mg plus ezetimibe 10 mg (Eze-Simva). (From Kastelein et al.[5], with permission).

gan to withdraw patients from ezetimibe therapy out of fear that continuing the drug would leave them exposed to litigation.

The best evidence to guide clinical decisions arises from randomized clinical event trials. Such data for ezetimibe will not be available before 2011 at the earliest (from the ongoing Improved Reduction of Outcomes: VYTORIN Efficacy International Trial [IMPROVE-IT]). However, it should also be pointed out that no data from *large-scale* clinical event trials are available that were designed to assess combinations of statin therapy with any other lipid-altering drug. Ezetimibe has been popular with physicians because of its favorable side effect profile, as well as its efficacy for lowering LDL-C, particularly as an adjunct to a statin. The National Cholesterol Education Program Third Adult Treatment Panel (NCEP ATP III) has consistently emphasized that LDL-C goal attainment is the primary focus of therapy in patients with dyslipidemia.[5,6] The use of ezetimibe significantly increases the number of high and very high risk patients able to attain their LDL-C goals.[7–11] It accounted for more than 15% of the total prescriptions for lipid therapy in the United States in 2006.[12] Moving ezetimibe to the "back of the line" would have substantial implications for lipid management. Therefore, careful consideration of the case for and against doing so is warranted.

Why did the ENHANCE trial fail to demonstrate a benefit?

An examination of the case for changing clinical practice would logically begin with an assessment of possible explanations for the negative results of the ENHANCE trial. The lack of benefit of adding ezetimibe to simvastatin therapy was surprising because other trials have found that more aggressive treatment of hypercholesterolemia results in slowed progression of CIMT.[13–17] For example, the Atorvastatin versus Simvastatin on Atherosclerosis Progression (ASAP) trial studied a group of 325 subjects with heterozygous familial hypercholesterolemia.[13] The results showed that more aggressive lowering of LDL-C with 80 mg/day of atorvastatin produced regression of CIMT (−0.031 mm), whereas the group that received less aggressive statin therapy (40 mg/day of simvastatin) showed progression of 0.036 mm ($P = 0.0001$ for the comparison between groups) (see Fig. 2). Given that this and other studies using the same methods of measurement have shown benefits of more aggressive LDL-C therapy, at least two potential explanations exist for the lack of benefit associated with ezetimibe treatment during the ENHANCE trial: 1) ezetimibe may not be antiatherogenic, despite its ability to lower LDL-C, atherogenic lipoprotein particles, and CRP, and 2) the participants in the ENHANCE trial may have had a lower than expected risk of progression, limiting the ability of the study to demonstrate a benefit.

Hypothesis 1: lack of efficacy

Ezetimibe could have as yet unidentified off-target adverse effects. Two types of compounds that lower LDL-C have previously failed to show benefits in clinical event trials: conjugated equine estrogens (with or without medroxyprogesterone acetate) and torcetrapib (a cholesteryl ester transfer protein inhibitor). However, these drugs also had off-target effects that might reasonably explain the lack of net benefit despite LDL-C reduction. Conjugated estrogens raise triglycerides and CRP, increase thrombogenicity,

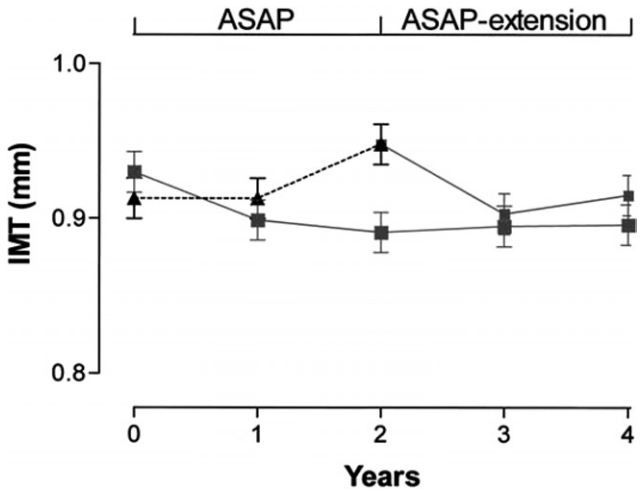

Figure 2 Mean (± SEM) values for carotid intima-media thickness in the Atorvastatin versus Simvastatin on Atherosclerosis Progression (ASAP) and ASAP-extension studies. *Squares* represent values for subjects who received 80 mg atorvastatin throughout and *triangles* represent values for subjects who received simvastatin 40 mg for the first two years and switched to atorvastatin 80 mg for the second two years. (From Van Wissen et al,[14] with permission).