EDITORIAL

ALLEN J. TAYLOR, MD*
Department of Medicine and Chief, Cardiology Service, Walter Reed Army Medical Center, Washington DC, and the Uniformed Services University of the Health Sciences, Bethesda, MD

Given the ENHANCE trial results, ezetimibe is still unproven

EZETIMIBE (Zetia) was licensed by the US Food and Drug Administration in 2002 on the basis of its ability to reduce low-density lipoprotein cholesterol (LDL-C) levels. The reductions are mild, approximately 15%,[1] which is comparable to the effects of a stringent diet and exercise or of a statin in titrated doses.

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However, there was no evidence that ezetimibe, which has a unique mechanism of action, delivers a benefit in terms of clinical outcomes. Despite this, the use of ezetimibe (alone or in fixed-dose combination with simvastatin, a preparation sold as Vytorin) grew rapidly, generating annual sales of $5.2 billion. Clinicians and the manufacturer (Merck/Schering-Plough) broadly assumed that LDL-C reduction would carry ezetimibe's day as clinical trials emerged.

The assumption seemed reasonable, since evidence from the past 3 decades has established a clear link between lowering LDL-C levels via diverse mechanisms and positive clinical outcomes, particularly lower rates of cardiovascular disease and death. Indeed, LDL-C measurement is now a focus of cardiovascular risk assessment and management, as reflected in national treatment guidelines.

THE ENHANCE TRIAL: EZETIMIBE FAILS A KEY TEST

Unexpectedly, ezetimibe failed its first step in clinical trial validation, the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial.[2] Apart from the scientifically irrelevant political regulatory intrigue generated by the sponsor's conduct in this trial, ENHANCE's findings challenge us to confront issues of what we assume vs what we really know, and how to interpret the complex results of clinical trials.

To be fair to the trial's investigators, ENHANCE achieved its objective of enrolling a population with a very high LDL-C level, which is ezetimibe's target and has been widely used in the study of atherosclerosis progression as a marker of potential drug benefit. Nevertheless, and even though the LDL-C level 2 years later was 52 mg/dL lower in the group receiving ezetimibe/simvastatin than in the group receiving simvastatin alone (Zocor), at LDL-C levels that are typically associated with atherosclerosis progression (140–190 mg/dL), ezetimibe failed to reduce the progression of atherosclerosis.

We should beware of explaining away results that do not match our expectations

In fact, after 2 years of therapy, the intima-media thickness had increased more in the ezetimibe/simvastatin group than in the simvastatin-only group, most notably in the most-diseased carotid and femoral segments, although the differences between groups were not statistically significant. A lack of effect or a trend toward a worse effect with ezetimibe was seen in 22 of 25 subgroups, including key subgroups based on prior statin treatment (patients with no prior statin therapy did not benefit), baseline carotid intima-media thickness (patients with thicker arteries did not benefit), and baseline LDL-C levels (those

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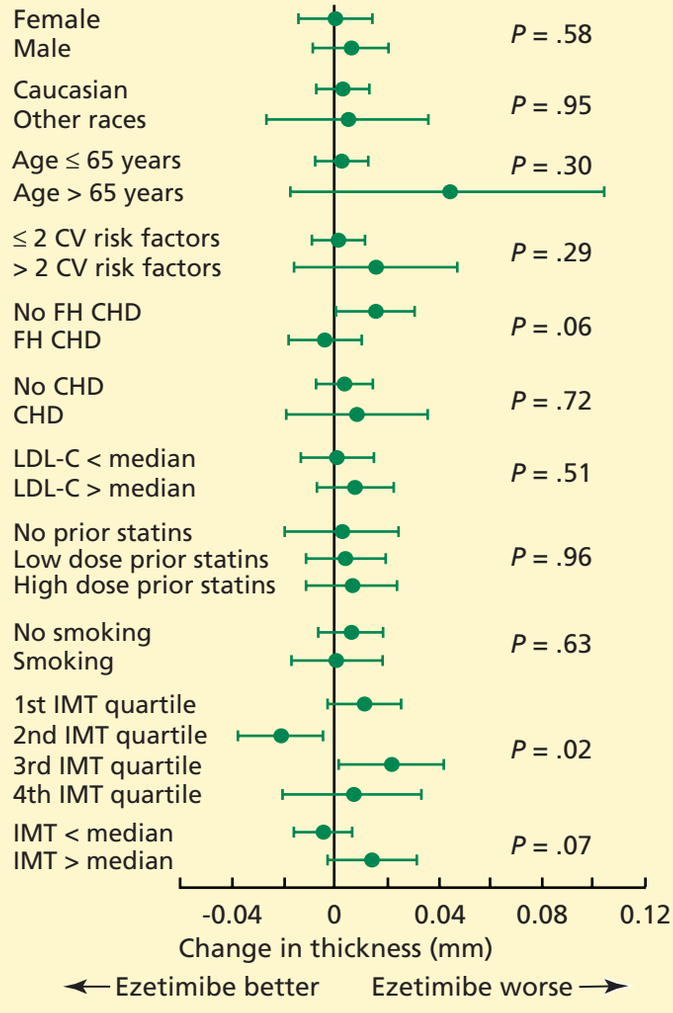

FIGURE 1. Differences in the change from baseline at 24 months in carotid intima-media thickness between patients treated with ezetimibe/simvastatin or simvastatin alone in prespecified subgroups in the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial. Bars = 95% confidence intervals, CV = cardiovascular, FH = familial hypercholesterolemia, CHD = coronary heart disease, LDL-C = low-density lipoprotein cholesterol, IMT = intima-media thickness.

SUPPLEMENTARY APPENDIX TO KASTELEIN JJ, AKDIM F, STROES ES, ET AL. SIMVASTATIN WITH OR WITHOUT EZETIMIBE IN FAMILIAL HYPERCHOLESTEROLEMIA. N ENGL J MED 2008; 358:1431–1443. DOI: 10.1056/NEJMoa0800742.

with higher baseline levels did not benefit) (FIGURE 1).

These trends are particularly worrisome, given that the ezetimibe/simvastatin group achieved a greater reduction in C-reactive protein levels, which typically has resulted in superior outcomes in atherosclerosis[3] and clinical effects[4] in combination with LDL-C reduction.

In view of these findings, should clinicians stand firm and continue to use ezetimibe? Or should we reevaluate our position and await more data about this unique, first-in-class compound?

WISHFUL POST HOC HYPOTHESES

In this issue of the *Cleveland Clinic Journal of Medicine*, Dr. Michael Davidson,[5] a respected lipid expert but one invested in ezetimibe's development, assures us that all is in order and that the results of ENHANCE can be explained away by several arguments, most notably that most of the trial's participants had previously received lipid-lowering treatment, which obscured the effects of ezetimibe. Moreover, he argues that ezetimibe's mechanism of action is well understood and that the drug is safe and well tolerated and thus should remain a first-line treatment for hyperlipidemia.

These arguments may eventually prove to be correct, but as of now they are merely wishful post hoc hypotheses awaiting more data apart from ENHANCE. Negative clinical trials do occur as a matter of chance, but we should be cautious in any attempts to explain away a trial that was designed, executed, and reported as conceived simply because the results do not match our expectations.

Confronted with ENHANCE, the astute clinician should ask three questions: Do we really understand ezetimibe's mechanism of action? Do other lines of evidence indicate the drug is beneficial? And how reliable is the arterial thickness as a surrogate end point?

DO WE UNDERSTAND EZETIMIBE'S MECHANISM OF ACTION?

Do we understand ezetimibe's full mechanism of action? Not really.

True, ezetimibe inhibits cholesterol transport, a process that is integral both to cholesterol's enteric absorption and to its systemic clearance. But although Dr. Davidson asserts

that ezetimibe has cellular effects similar to those of statins, in fact it has the opposite effect on HMG-coA reductase, and no effects on LDL receptors.[6]

Furthermore, although initial studies suggested that ezetimibe inhibits enteric cholesterol absorption by inhibiting the Niemann-Pick C1L1 (NPC1L1) receptor, more recent investigations call this into serious question and point more definitively at a receptor known as scavenger receptor-B1 (SR-B1). As stated in a recent editorial, "SR-B1 in the apical site of enterocytes is the primary high-affinity site of cholesterol uptake and ezetimibe can inhibit this process. Moreover, the [possibility is ruled out] of NPC1L1 being a major player in this cholesterol uptake. This is at variance with the view of the colleagues from Schering-Plough who claim the same for NPC1L1."[7]

SR-B1 is also a high-affinity receptor for high-density lipoprotein[8] and thus is active in the antiatherosclerotic process of reverse cholesterol transport, inhibition of which significantly accelerates the development of atherosclerosis.[9]

Statins, but not ezetimibe, boosted arterial response to acetylcholine

Additionally, in vitro and thus unrelated to the effects of changing cholesterol concentration, ezetimibe down-regulates SR-B1 and another key cholesterol transporter protein called ABCA1.[10] Further, ezetimibe induces down-regulation of raft protein domains, including CD36,[11] another effect opposite to that of statins.

These little-recognized effects of ezetimibe are among many that are completely unrelated to enteric cholesterol absorption. Yet, they are likely to be active within the liver and systemically where these proteins reside, and they are putatively proatherosclerotic. Contrary to often-cited opinion, ezetimibe is systemically absorbed, with 11% of the compound excreted in the urine.[12] Thus, the compound is systemically available to exert these same actions in the liver and elsewhere. Moreover, the absorbed drug is glucuronidated and is extensively recirculated in the liver in a form (its glucuronide) that is more potent than the parent compound.

In sum, present opinion is that ezetimibe inhibits lipid transport and interacts with a variety of receptors, not only in the gut but also systemically at the cell membrane and also inside the cell, focally disrupting several tightly regulated biologic processes.[7] Thus, although ezetimibe reduces serum LDL-C levels via its effect in the gut, this effect may well be offset or even overridden systemically by other, unmeasurable effects, leading to counterintuitive results in terms of atherosclerosis or clinical events.

This would not be the first time a lipid-lowering drug has disappointed us: torcetrapib, another transport inhibitor, dramatically raises serum high-density lipoprotein cholesterol levels and reduces LDL-C but was found not only to have no effect on atherosclerosis, but also to potentiate adverse clinical outcomes.

The net impact of these other actions of ezetimibe is not known. We will discover its true clinical effects only through studies of endothelial function, atherosclerosis, and clinical cardiovascular outcomes. ENHANCE, which looked at atherosclerosis, is thus our strongest signal to date on the net effect of ezetimibe.

DO OTHER LINES OF EVIDENCE INDICATE EZETIMIBE IS BENEFICIAL?

Can we be reassured that ENHANCE's results are spurious on the basis of other lines of evidence? Again, not really.

Experiments in animals, particularly in mice,[13] have shown that ezetimibe may be antiatherosclerotic, although mice are considered the "worst model"[7] for the study of ezetimibe, and notably, LDL-C levels were lowered far more in these experiments than they are clinically. Enthusiasm for these animal models should be tempered by interspecies variability in ezetimibe's "off-target" effects and in the recent failure of other lipid transport drugs in human trials (torcetrapib and ACAT inhibitors) that had shown initial success in animals. No animal model is established for evaluating drugs of ezetimibe's class, given its complex mechanism of action.

In human studies, the only other surrogate of the net effect of ezetimibe is endothelial function. Among several randomized clinical trials of ezetimibe,[14–18] only one was designed to compare the effects of ezetimibe

alone, ezetimibe plus a statin, and a statin by itself in titrated or in maximum doses.[15] After 4 weeks of therapy, all groups had lower LDL-C levels. However, ezetimibe monotherapy and ezetimibe/simvastatin combination therapy had no detectable effect on the arterial response to acetylcholine, but atorvastatin (Lipitor) monotherapy did. To be fair, the other (very small) trials showed mixed results, thus keeping the hypothesis of ezetimibe's benefit alive, but with nothing close to a clear signal of benefit.

IS ARTERIAL THICKNESS RELIABLE AS A SURROGATE END POINT?

Was the principal problem in ENHANCE the use of carotid intima-media thickness as the primary end point? No.

This issue has received a lot of attention, much of which I believe is misinformed. No trial end point is infallible, including carotid intima-media thickness, and one must remain open to the possibility of chance findings. However, it has been a relatively reasonable end point in trials of diverse cardiovascular preventive strategies, including lipid-lowering, blood-pressure-lowering, and lifestyle interventions and as a directional biomarker of clinical atherosclerotic events.

We should be cautious about comparing data on carotid intima-media thickness from different trials, as Dr. Davidson attempts to do, in view of methodologic and population differences: each trial must be considered independently. Of greatest concern in ENHANCE is the consistency among intima-media thickness end points, including strong trends toward adverse effects in the most diseased carotid and femoral segments.

Moreover, ENHANCE's detractors contend that the carotid intima-media thickness of the studied population was normal, citing this as evidence of delipidation from prior treatment. Although not impossible (as shown by the work of Zhao and colleagues in the setting of prolonged, intense lipid-lowering therapy[19]), at the moment this hypothesis is a matter of conjecture in the ENHANCE participants, particularly because their LDL-C levels were still quite elevated during the trial and conceivably even before randomization.

But these patients were *not* normal: they were typical patients with familial hypercholesterolemia with extremely elevated LDL-C levels and abnormally thick arteries for their age. Population screening estimates show that, for age and sex, the carotid intima-media thickness values in ENHANCE would lie in the upper quartile of those in the general population.[20] Moreover, their mean value is consistent with that in similar-aged groups of patients with familial hypercholesterolemia, even with lower rates of prior statin pretreatment.[21]

The most convincing evidence for the validity of the ENHANCE findings comes from the published subgroup data (**FIGURE 1**). In participants whose baseline carotid intima-media thickness was above the median at baseline, the thickness increased more with ezetimibe/simvastatin than with simvastatin alone. The same was true in the subgroup with above-average LDL-C levels at baseline. The subgroups with no prior statin treatment, low-dose prior statin treatment, and high-dose prior statin showed no heterogeneity of response: their carotid intima-media thickness increased more with ezetimibe/simvastatin than with simvastatin alone. None of these differences was statistically significant; however, these prespecified subgroup data seemingly invalidate arguments against the ENHANCE results based on carotid intima-media thickness findings.

In this context, ENHANCE can only be interpreted as a strong initial negative signal, a "red flag" about ezetimibe's net health benefits.

'Safe and well-tolerated' is not enough—a drug must show clinical benefit

WHAT NEXT?

The proper present focus of this debate is not on LDL-C but rather on ezetimibe, its unique mechanism of action, and on the need for more evidence about this complex compound.

At present, ezetimibe's mechanism of action is not fully understood, and its benefit—for now, only mild LDL-C reduction—is too uncertain for us to be spending $5.2 billion a year for it. Its manufacturer is fortunate that the drug is even licensed, given the current and seemingly appropriate regulatory changes under which drugs introducing new therapeutic classes are scrutinized more closely for ben-

efits and risks. "Safe and well tolerated," as contended by Dr. Davidson, is not nearly enough: drugs must show clinically important benefits. We still know too little about this drug, the manufacturer of which has invested far more in marketing than in science, a point on which Dr. Davidson and I agree.

In 2008, ezetimibe is an appropriate candidate for testing in clinical trials, and in years to come it may be worthy of clinical attention—if rigorous and objectively conducted clinical trials prove its worth. At present, clinical equipoise dictates that ezetimibe is not an appropriate alternative to a statin in titrated doses, to the addition of other lipid-lowering drugs to a statin, to greater attention to drug adherence, or to lifestyle modification.

For the moment, given the ENHANCE results, the clinical usefulness of ezetimibe still remains to be proven. Much more evidence is needed before we can confidently reembrace the clinical use of ezetimibe. ■

The manufacturer 'has invested far more in marketing than in science'

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ADDRESS: *Allen J. Taylor, MD, Chief, Cardiology Service, Walter Reed Army Medical Center, 6900 Georgia Ave., NW, Building 2, Room 4A34, Washington, DC 20307-5001; e-mail allen.taylor@na.amedd.army.mil.*