COMMENTARY

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INTERPRETING THE ENHANCE TRIAL

Is ezetimibe/simvastatin no better than simvastatin alone? Lessons learned and clinical implications

THE EZETIMIBE AND SIMVASTATIN in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial[1] was probably the most widely publicized clinical study of the past decade. How did a 720-patient imaging trial with a neutral result in patients with severe hypercholesterolemia rise to a level warranting massive media attention, a congressional investigation, and a recommendation to curtail the use of a drug widely used to reduce levels of low-density-lipoprotein cholesterol (LDL-C)?

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The reaction to the ENHANCE trial reveals more about the political climate and the relationship between the pharmaceutical industry and the American public than it does about the effects of ezetimibe (available combined with simvastatin as Vytorin and by itself as Zetia) on the progression of atherosclerosis.

SOME SELF-DISCLOSURE

Before I discuss the clinical implications of the ENHANCE trial, I must describe both my financial conflicts and intellectual biases. I am a paid consultant, speaker, and researcher on behalf of Merck/Schering-Plough, the sponsor of the ENHANCE trial. I was a principal investigator in the first phase II trial of ezetimibe and have conducted more than 10 clinical trials of either ezetimibe or ezetimibe/simvastatin. I also have been a strong advocate for imaging trials to assist in the clinical development of novel therapeutic agents and to support regulatory approval.

Therefore, I believe that the thickness of the intima and media layers of the carotid arteries is a useful surrogate to evaluate the potential antiatherosclerotic effects of drugs (more on this topic below). Also, I believe that the LDL-C-lowering hypothesis has been proven: ie, that all drugs that lower LDL-C safely, without off-target adverse effects, should reduce cardiovascular events. I support the goal levels of LDL-C and non-high-density-lipoprotein cholesterol set by the National Cholesterol Education Program's third Adult Treatment Panel (ATP III) guidelines,[2,3] which specify LDL-C targets rather than the use of specific drugs. In spite of these conflicts and potential biases, I believe I have always served the best interests of patient care.

The reaction to ENHANCE says more about the political climate than about ezetimibe

HISTORY OF THE ENHANCE TRIAL

The ENHANCE trial was designed in early 2000 by John J. Kastelein, MD, PhD, one of the most prominent clinical trialists in lipidology,[4] and the protocol was finalized in April 2002. The trial was designed to evaluate the effects of two regimens: ezetimibe 10 mg

*Dr. Davidson has disclosed that he has received consulting fees, honoraria, or grant support from Abbott Laboratories, Access Health, AstraZeneca Pharmaceuticals, Atherogenics, Daiichi-Sankyo, diaDexus, Kinemed, Merck & Co, Merck/Schering-Plough, Oscient Pharmaceuticals, Pfizer Laboratories, PreEmptive Meds, Roche Pharmaceuticals, sanofi-aventis, Synarc, and Takeda Pharmaceuticals for consulting, speaking, research, or serving on advisory boards. He also owns equity in or is on the board of directors of Angiogen, Professional Evaluation Inc, Medical Education Company, and Sonogene.

Glossary of other trials discussed in this article

ACTIVATE[32]—ACAT Intravascular Atherosclerosis Treatment Evaluation

ARBITER[27]—Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol

ASAP[28]—Atorvastatin vs Simvastatin on Atherosclerosis Progression

ASTEROID[37]—A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden

CAPTIVATE—Efficacy and Safety of the ACAT Inhibitor CS-505 (Pactimibe) for Reducing the Progression of Carotid Artery Disease

CORONA[38]—Controlled Rosuvastatin Multinational Trial in Heart Failure

IMPROVE-IT—Improved Reduction of Outcomes: Vytorin Efficacy International Trial

JUPITER—Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin

METEOR[26]—Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin

PROVE-IT[39]—Pravastatin or Atorvastatin Evaluation and Infection Therapy

RADIANCE[31]—Rating Atherosclerotic Disease Change by Imaging With a New CETP Inhibitor

SEAS—Simvastatin and Ezetimibe in Aortic Stenosis

SHARP—Study of Heart and Renal Protection

One expert's view: 'Ezetimibe is an expensive placebo'

plus simvastatin 80 mg vs simvastatin 80 mg (Zocor) in 720 patients with familial hypercholesterolemia and an LDL-C level of at least 210 mg/dL after stopping all lipid therapies. In fact, after the placebo run-in period, the mean total cholesterol value was 400 mg/dL, and the mean LDL-C value was about 318 mg/dL.

The end point defined as the mean of six measurements

The primary end point was the change in the thickness of the intima and media layers of the carotid arteries over a 2-year period, measured by ultrasonography. A composite measure was used: the mean of the thicknesses in the far walls of the right and left common carotid arteries, the right and left carotid bulbs, and the right and left internal carotid arteries. Secondary end points included the change in the mean maximal carotid artery intima-media thickness (ie, the thickest of the six baseline measurements), the proportion of participants who developed new carotid artery plaque (defined arbitrarily as an intima-media thickness > 1.3 mm), and changes in the mean of the intima-media thickness of the six carotid sites plus the common femoral arteries.

The last participant completed the trial in April 2006. Reading of the almost 30,000 scans was not started until the last participant was finished, so that all scans for each participant could be read in a blinded, randomized order by five separate readers. A significant proportion of the images that the protocol called for could not be obtained or analyzed, particularly in the internal carotid artery and the carotid bulb, which are often difficult to visualize. As a result, 17% of the internal carotid or carotid bulb measurements were discarded.

To change the end point post hoc, or not to change the end point?

The sponsor of the trial was concerned about the missing data points and convened a special advisory board to review the blinded data. This group suggested a solution: changing the primary end point from the six-site composite value to the mean value in just the common carotid arteries. They based this suggestion on the greater success rate in measuring the common carotids (97%) than in measuring all six sites (88%), as well as on recent trials that indicated that the common carotid artery

measurement correlates better with clinical outcomes (because the internal carotid and the bulb measurements vary more). On November 26, 2007, Merck/Schering-Plough announced the primary end point would be changed to the mean change in the common carotid arteries.

However, during a separate meeting on November 30, 2007, some members of the Merck/Schering-Plough advisory board objected to the change. On December 11, 2007, the company announced that the original primary end point would not be changed.

Neutral results, negative publicity

On December 31, 2007, the ENHANCE study was unblinded, and on January 14, 2008, Merck/Schering-Plough issued a press release announcing the results. The press release stated that there were no statistically significant differences between the treatment groups in the primary end point or in any of the secondary end points, despite a 16.5% greater reduction in LDL-C (about 50 mg/dL) in the group receiving the ezetimibe/simvastatin combination. The composite intima-media thickness had increased by an average of 0.0111 mm in the combined-therapy group vs 0.0058 mm in the simvastatin-only group (P = .29) over the 24-month treatment period.[5]

The press release received unprecedented international media attention. One leading cardiologist commented to the media that ENHANCE showed "millions of patients may be taking a drug [ezetimibe] that does not benefit them, raising their risk of heart attacks and exposing them to potential side effects."[6] The perceived message that ezetimibe/simvastatin is harmful resulted in thousands of phone calls from concerned patients to their physicians throughout the United States. The American Heart Association (AHA) and the American College of Cardiology (ACC) issued a joint statement the next day saying that ezetimibe/simvastatin does not appear to be unsafe and that patients should not stop taking the drug on their own. In the following days, Merck/Schering-Plough placed advertisements in newspapers reaffirming the safety of ezetimibe and quoting the AHA/ACC statement.

But the full results of the study were not available at that point. In fact, Senator Charles Grassley (R-Iowa) had launched a congressional investigation into the delays in releasing the results of the ENHANCE trial in December 2007. A focus of the investigation was whether the sponsor was delaying the release either because the data reflected negatively on its product or because it was legitimately concerned about the quality of the measurements of the carotid intima-media thickness. After Merck/Schering-Plough placed the advertisements quoting the AHA/ACC statement, these organizations were criticized for touting the safety of ezetimibe while receiving educational grants and other funds from Merck/Schering-Plough. Senator Grassley sent a letter to the ACC in late March requesting information about the amount of funds the ACC had received.

Full results are published, and the ACC is misquoted

The ENHANCE study was selected for a special presentation at the ACC annual scientific session on March 30, 2008. The full ENHANCE results were presented by Dr. Kastelein, after which an expert panel led by Harlan M. Krumholz, MD, discussed the trial's implications. The ENHANCE results were simultaneously published in the *New England Journal of Medicine*,[1] accompanied by an editorial by B. Greg Brown, MD, and Allen J. Taylor, MD,[7] and another editorial by the editors of that journal, Jeffrey M. Drazen, MD, and colleagues.[8] The expert panel and the editorialists concluded that the ENHANCE trial data raised concerns about the cardiovascular benefits of ezetimibe; that statins should be used as initial therapy for hyperlipidemia and titrated to the goal LDL-C level or to the maximally tolerated dose; and that other drugs such as bile acid sequestrants, fibrates, and niacin should be used in combination with statins before considering ezetimibe.[9]

Thousands of concerned patients called their physicians

The next day, stories appeared in the media mistakenly stating that the ACC had recommended that ezetimibe/simvastatin be discontinued. This view was fueled by an article in the ACC's *Scientific Session News*, penned by a contract writer and editor, with the headline, "ACC on Vytorin: Go Back to Statins" that said, "After waiting for 18

months for the results of the ENHANCE study, an ACC panel on Sunday encouraged physicians to use statins as a first line and prescribe Vytorin only as a last resort for patients unable to tolerate other cholesterol-lowering agents."[10]

The ACC later clarified that this was the opinion of the panelists and not that of the ACC, and they reiterated statements from the AHA/ACC Secondary Prevention Guidelines[11] recommending statins in maximally tolerated doses or titrated to a goal LDL-C level for first-line drug treatment of coronary artery disease, and recommending that patients speak with their physicians before discontinuing any therapy.

WHY WERE THE ENHANCE STUDY RESULTS NEUTRAL?

The ACC expert panel concluded that the most likely reason for the neutral ENHANCE results was that ezetimibe lowers LDL-C but does not confer a cardiovascular benefit. In the words of Dr. Krumholz (as quoted by Shannon Pettypiece and Michelle Fay Cortez on bloomberg.com), ezetimibe is "just an expensive placebo."[12]

Ezetimibe, statins, and bile acid sequestrants all up-regulate LDL receptors

There are at least three potential explanations for the lack of benefit with ezetimibe in the ENHANCE trial. I list them below in order of lowest to highest probability, in my opinion:

Theory 1: Ezetimibe lowers LDL-C but is not antiatherogenic

Since almost all experts agree that lowering LDL-C confers cardiovascular benefits, if ezetimibe does not inhibit atherosclerosis it must have some "off-target" effect that negates its LDL-C-lowering benefit. Critics of ezetimibe point out that oral estrogen and torcetrapib also lower LDL-C but do not improve cardiovascular outcomes.[13,14]

The lack of benefit with these two other agents can be explained. Oral estrogen does not lower apolipoprotein B (an indication of the number of atherogenic particles), but rather it increases the levels of both triglycerides and C-reactive protein, and it is prothrombotic in some people.[15] Torcetrapib increases aldosterone production and substantially raises blood pressure.[16] Therefore, both drugs have true off-target effects that could explain their failure to reduce cardiovascular risk despite reductions in LDL-C. (Interestingly, though, oral estrogen has been shown to slow the progression of carotid intima-media thickness in newly postmenopausal women.[17]

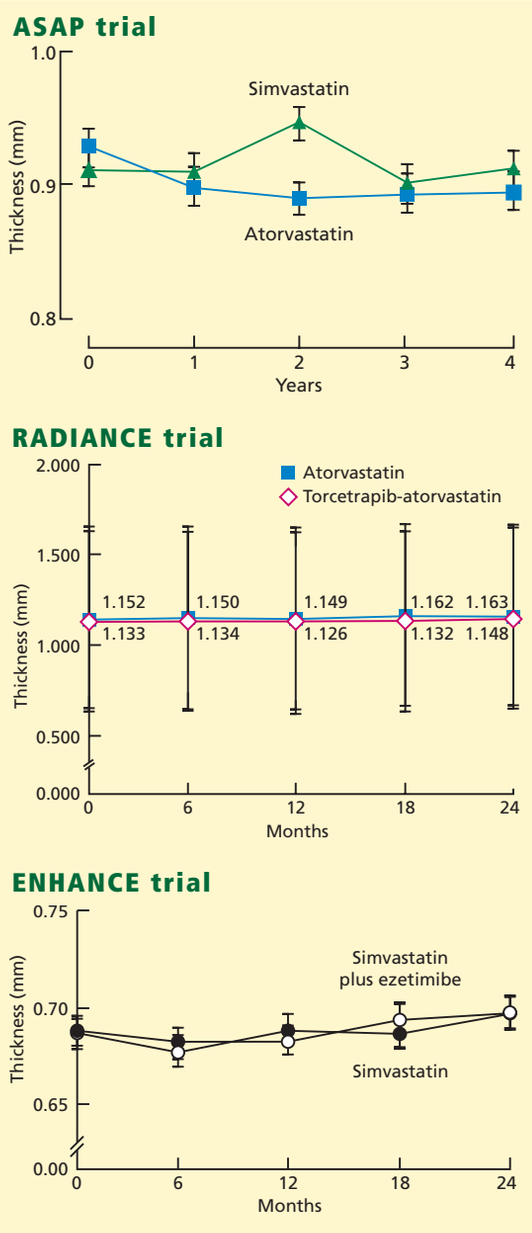
Ezetimibe, however, lowers LDL-C by an ultimate mechanism similar to that of statins and bile acid sequestrants, ie, by up-regulating LDL receptors, although these drugs reach this mechanism via different pathways. Statins inhibit cholesterol synthesis, thereby lowering hepatic intracellular cholesterol and thus up-regulating LDL-receptors and enhancing LDL-C clearance from the plasma. Bile acid sequestrants interrupt bile acid reabsorption in the ileum, thereby decreasing intracellular hepatic cholesterol and up-regulating LDL receptors. Ezetimibe, like bile acid sequestrants, also decreases cholesterol return to the liver, lowering hepatic intracellular levels and thus up-regulating LDL receptors.[18]

Ezetimibe is unlikely to have an off-target effect because it is only fractionally absorbed systemically, and a recent animal study showed that it enhances macrophage efflux of cholesterol, thereby potentially increasing reverse cholesterol transport.[19] Ezetimibe has also been shown to reduce atherosclerosis in animal models.[20]

In their editorial, Drs. Brown and Taylor[7] noted that ezetimibe reduces the expression of adenosine triphosphate binding cassette A1 (ABCA1) in Caco-2 (an intestinal cell line), and this may be an example of an off-target effect. However, statins also reduce ABCA1 expression in macrophages.[21] ABCA1 is sensitive to intracellular cholesterol, and when cholesterol levels are decreased, whether by statins or by ezetimibe, ABCA1 expression is down-regulated.[22]

Theory 2: Intima-media thickness does not reflect the true benefits of lowering LDL-C

The carotid intima-media thickness is a surrogate end point that predicts coronary events and the rate of progression of coronary atherosclerosis.[23] In trials of lovastatin (Mevacor),[24] pravastatin (Pravachol),[25] and rosuvastatin (Crestor),[26] the carotid intima-media was thinner at 24 months with the active drug than with placebo. In two relatively small tri-



After 2 years of statins, atherosclerosis may stop regressing

FIGURE 1. Top, in the ASAP extension study, the carotid intima-media thickness did not decrease further after 2 years of treatment with high-dose atorvastatin. This may explain the lack of regression in the RADIANCE (**middle**) and ENHANCE trials (**bottom**), in which most patients had already been on long-term statin therapy.

als—ARBITER 1 (n = 161),[27] which was open-label, and ASAP (n = 325)[28,29]—aggressive lipid-lowering reduced the progression of intima-media thickness better than less-aggressive therapy. However, this measure has been used to evaluate the effects of differing degrees of LDL-C reduction between active treatments in fewer than 500 research participants.

Furthermore, what part or parts of the carotid system are we talking about? In recent trials led by Dr. Kastelein, the intima-media thickness of the common carotid arteries increased with pactimibe (an acyl-coenzyme A:cholesterol O-acyltransferase, or ACAT, inhibitor)[30] and torcetrapib,[31] but the six-site composite measure (which was the primary end point in these trials, as in ENHANCE) did not increase more than in the control groups. Pactimibe was also shown to increase atheroma volume as measured by intravascular ultrasonography in the ACTIVATE trial.[32] Therefore, the thickness of the common carotid arteries has been shown to be a better predictor of harm from a therapy than the composite measurement.

The advantage of measuring the common carotid artery is that it is easier to visualize and measure, and therefore the measurements vary less. In the METEOR trial,[26] the six-site measurement increased significantly less with rosuvastatin than with placebo, but the common carotid measurement alone was more strongly associated with a difference in progression. In the ENHANCE trial, the thickness of the common carotid arteries increased by 0.0024 mm with simvastatin alone vs 0.0019 mm with simvastatin/ezetimibe, a difference of 0.005 mm that was not statistically significant (P = .93).[1]

Although the six-site measurement appears to be good for predicting coronary events and evaluating therapies, the measurement in the common carotid arteries appears to be a more reliable surrogate end point for predicting both benefit and harm from antiatherogenic agents. However, trials of statins and other lipid-lowering therapies that assessed clinical events have shown that the reduction in risk associated with a given reduction in cholesterol is similar regardless of the mechanism by which cholesterol is low-

ered.[33] Therefore, the LDL-C level is far superior as a marker of clinical benefit.

Theory 3: Previous statin treatment affected the ENHANCE results

By far the most likely explanation for the neutral findings in ENHANCE is that the patients were so well treated before entry that it was impossible to detect a difference between the two treatment groups in carotid intima-media thickness at the end of the study. Eighty percent of the patients had received statins previously, and at baseline the mean intima-media thickness of the common carotid arteries was only 0.68 mm.[1] In contrast, most other trials required a thickness greater than 0.7 mm for entry.

The two main reasons for selecting a population with familial hypercholesterolemia were the assumptions that these participants would have a greater-than-average carotid intima-media thickness at baseline and that they would show an above-average progression rate, even on high-dose statin therapy.[4] Both of these assumptions were incorrect: the baseline thickness was normal and the progression rate was negligible in both groups.

The ENHANCE trial design was based on the smaller ASAP trial,[28,29] which found a significant reduction in progression of carotid intima-media thickness with atorvastatin (Lipitor) in high doses compared with simvastatin in lower doses. However, the ASAP patients had to have had a common carotid intima-media thickness greater than 0.7 mm to enter. A follow-up study after the initial treatment period[29] showed minimal subsequent progression (0.005 mm/year) with atorvastatin 80 mg/day (FIGURE 1), suggesting that further lowering of LDL-C may have minimal impact on the progression of carotid intima-media thickness after a period of statin treatment. Since 80% of the ENHANCE patients were previously treated with statins, adding ezetimibe to high-dose simvastatin therapy may have been unlikely to affect the progression of carotid intima-media thickness.

Accordingly, the high prevalence of statin pretreatment and the near-normal carotid intima-media thickness at baseline may have prevented the 16.5% greater reduction in LDL-C due to ezetimibe from producing a difference in progression over 24 months of treatment. This conclusion is supported by the long-term follow-up results from ASAP, RADIANCE 1, and CAPTIVATE, all of which showed that in patients with familial hypercholesterolemia well treated with statins, progression of carotid intima-media thickness is negligible.[30,31]

Further supporting this view, in a previous trial by Dr. Kastelein's group in patients with familial hypercholesterolemia,[34] giving simvastatin 80 mg for 2 years decreased the intima-medial thickness by .081 mm ($P < .001$), compared with 0.0058 mm in ENHANCE (a 14-fold difference). In the previous trial, the baseline measurement was 1.07 mm (vs 0.68 mm in ENHANCE), and the extent of the change was significantly associated with the baseline measurement ($r = .53$, $P < .001$) but not with the change in LDL-C levels.

This is powerful evidence that, in two similar studies that used the same methodology and the same drug, the thinner arteries in the ENHANCE trial are by far the most likely explanation for the lack of change with the addition of ezetimibe to high-dose simvastatin. The METEOR trial enrolled only patients who had never received statins and whose carotid intima-media was thicker than 1.2 mm. In retrospect, a similar design would have been preferable for ENHANCE.[35]

80% of ENHANCE patients had received statins, and their carotid thickness was low at baseline

LESSONS LEARNED AND CLINICAL IMPLICATIONS

For Merck/Schering-Plough, missed opportunities

Although Dr. Krumholz (the spokesman for the ACC panel discussion) and I disagree on the clinical implications of the ENHANCE trial, we do agree on an important point. Dr. Krumholz posed the question that if the LDL-C-lowering hypothesis was already proven for ezetimibe, why was the ENHANCE trial conducted? After 6 years on the market, the efficacy of ezetimibe on cardiovascular outcomes should already have been established. It should not take this long to determine the clinical outcome benefit for a drug.

Merck/Schering-Plough's outcome program for ezetimibe was inadequately designed to demonstrate the clinical value of this novel compound. Rather than assuming the LDL-C-

lowering hypothesis was already established, they conducted another "lower-is-better" trial with the carotid intima-media thickness as the end point, and they succeeded only in raising doubt about the benefits of ezetimibe rather than showing that dual therapy is at least equivalent to high-dose statin therapy.

A preferable approach would have been to compare the effects of a statin in low doses plus ezetimibe vs high-dose statin monotherapy on either surrogate or hard outcomes. If the low-dose statin/ezetimibe combination, which should lower the LDL-C level as much as high-dose statin monotherapy, could provide similar or better outcomes with fewer side effects, this trial would change our practice.

One had hoped that dual therapy, by reducing both intestinal cholesterol absorption and hepatic synthesis of cholesterol, would improve outcomes by modifying postprandial chylomicron composition or by reducing plant sterol absorption.[36] Unfortunately, other outcome trials of ezetimibe/simvastatin will not provide an answer regarding the potential advantages of dual therapy. The SEAS study is comparing the number of clinical events in patients with aortic stenosis who receive ezetimibe/simvastatin or placebo; SHARP is being conducted in patients with chronic kidney disease. Although both groups of patients have high rates of coronary events, these trials will not address whether adding ezetimibe provides additional benefits. In fact, if the results of these trials turn out neutral, as in ENHANCE, then ezetimibe will be blamed for potentially offsetting the benefits of simvastatin, and if the trials show a benefit, the simvastatin component of ezetimibe/simvastatin will be given the credit.

The lure of 'pleiotropic effects' distracts many of us from LDL-C reduction

The answer may come in 3 to 4 years with the results of IMPROVE-IT, a study of 18,000 patients with acute coronary syndrome treated with ezetimibe/simvastatin or simvastatin. The simvastatin monotherapy group will have a target LDL-C level of less than 80 mg/dL and the ezetimibe/simvastatin group will have an LDL-C target about 15% less. Although this trial is testing the lower-is-better hypothesis with ezetimibe, if the study does not show a benefit, it may not be because ezetimibe lacks clinical efficacy but rather because the LDL-C effect is curvilinear, and there is minimal further benefit of lowering the LDL-C level past 70 mg/dL. If the results of the IMPROVE-IT trial are negative, it may mean the end of ezetimibe as an LDL-C-lowering drug.

Merck/Schering-Plough has lost valuable time in not demonstrating the benefits of ezetimibe on clinical events. In contrast, consider rosuvastatin, an AstraZeneca product. Rosuvastatin was approved about the same time as ezetimibe/simvastatin, and 6 years later it has already received a label change for the reduction of progression of atherosclerosis, based on positive outcomes in the METEOR trial,[35] the ASTEROID intravascular ultrasonography trial,[37] and the CORONA trial (an important trial that examined hard clinical end points).[38] More importantly, the JUPITER trial was recently stopped early owing to a reduction in cardiovascular deaths. Initially, rosuvastatin received an unfair media portrayal as an unsafe drug. Now, because of its proven benefits in outcome trials, it will receive more widespread consideration for clinical use.

For preventive cardiologists, a painful reminder to focus on LDL-C

For the preventive cardiologist or lipidologist, the ENHANCE trial has been a painful reminder that despite overwhelming evidence, the mantra of "the lower the LDL-C the better" is still not universally accepted. We acknowledge the great benefits of statins, but the lure of "pleiotropic effects" distracts many of us from the necessity of more aggressive LDL-C reduction.

The pleiotropic benefits of statins were first raised as a means of supporting increased clinical use of pravastatin vis-a-vis other, more efficacious statins. It was not until the PROVE-IT study that pravastatin's pleiotropic effects were found not to translate into a benefit equivalent to that of the more efficacious statin, atorvastatin.[39]

The success of ezetimibe was its ability to safely and easily lower LDL-C in combination with statins to achieve treatment goals. For many patients, a lower-dose statin and ezetimibe together provide a well-tolerated and efficacious approach to treating hyperlipidemia. The fallout from the ENHANCE trial is that many patients who were well treated or who could be better treated with ezetimibe in

combination with a statin will not receive the best tolerated regimen. In fact, preliminary prescription data after the release of the ENHANCE study support our worse fear, ie, that patients at high risk will receive less aggressive LDL-C reduction. Since the ENHANCE data were released, more than 300,000 patients have stopped taking either ezetimibe/simvastatin or ezetimibe, and nearly all have continued on generic simvastatin or on a dose of statin with less overall efficacy.

An example is Senator John McCain, who, according to his recently released medical records, has a Framingham 10-year risk of more than 20% and was on ezetimibe/simvastatin to treat an elevated cholesterol level. After release of the ENHANCE trial, he was switched to generic simvastatin, and his LDL-C increased from 82 mg/dL to 122 mg/dL. He most likely has an LDL-C goal of less than 100 mg/dL according to the ATP III guidelines, and he is therefore no longer at his target.

For physicians in the community, questions from concerned patients

For the physicians who have received hundreds of phone calls and e-mails from concerned patients, the ENHANCE trial results must have been both discouraging and confusing. At present, I think we should remember the following:

- Ezetimibe's mechanism of action is well understood
- It is safe and well-tolerated
- It still has a role as an add-on to statin therapy (or as monotherapy or combined with other agents in those who cannot tolerate statins) for patients who have not yet achieved their LDL-C target.

For the pharmaceutical industry, enormous challenges

The neutral ENHANCE trial results created an uncomfortable situation for the trial sponsor. A heavily marketed drug failed to achieve its expected result after the study results were delayed for a few months. The pharmaceutical industry ranks 14th out of 17 industries in public trust among the American public, and this study provided an opportunity for its critics to attack what is, in their opinion, an overly marketed drug.

Enormous challenges are on the horizon for the pharmaceutical industry, with a shrinking pipeline of potential new drugs, increasing regulatory hurdles, greater liability risk, political pressure for price controls, enhanced scrutiny of sales practices, and a growing media bias. As a cardiologist and clinical researcher whose father died at age 47 of a myocardial infarction, I am concerned that, unless change occurs, a vibrant pharmaceutical industry with the financial and intellectual capital to find and develop new, more effective treatments will cease to exist.

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