Editor’s Perspective

Emphasizing the Burden of Proof
The American College of Cardiology 2008 Expert Panel Comments on the ENHANCE Trial
Harlan M. Krumholz, MD, SM

In March 2008, I had the honor of participating on a panel with Drs Joseph Messer, Rick Nishimura, and Patrick O’Gara, all exemplary clinicians and teachers, to discuss the results of the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial at the American College of Cardiology annual Scientific Session. The meeting was full of expectation for this trial, which compared the effect of simvastatin plus ezetimibe with simvastatin alone on the progression of carotid artery intima-media thickness. Anticipation was intensified because of the controversy that accompanied delays in the publication of the trial results.1 Our panel had early access to the results and discussed the findings. When our discussions led to a consensus of opinion, we decided to present a single statement rather than 4 distinct views. I was asked to draft the statement, which was discussed and approved by the panel, and present it at the Scientific Session.

ENHANCE, presented at the Session by Dr John Kastelein, failed to demonstrate that the addition of ezetimibe to simvastatin reduced the progression of carotid thickness compared with simvastatin alone.2 The result prompted our panel to question what could be inferred about the effect of ezetimibe on clinical outcomes, given the current body of evidence. The statement emphasized that it was not possible to know at this point whether ezetimibe was beneficial, harmful, or without a clinically important effect. We recognized low-density lipoprotein (LDL) as a strong predictor of outcomes and that ezetimibe reduced LDL, but felt the need to emphasize that the clinical effect of a drug cannot be inferred based solely on its effect on a biomarker. The point was not that ENHANCE indicated a failure of ezetimibe, but that ENHANCE opened our eyes to the lack of data about the clinical effect of ezetimibe.

Our statement followed Dr Kastelein’s presentation. Although it was never officially published, the statement heralded an important change in perspective regarding drugs and interventions that have known effects on selected biomarkers, but unknown effects on patient outcomes. Its themes resonate as we increasingly focus on the comparative effectiveness of strategies that produce the same effect on biomarkers but potentially different effects on patients. So, for the record, I present the remarks on the ENHANCE trial presented on March 30, 2008, at the annual Scientific Session of the American College of Cardiology:

Sometimes negative studies can provide very important insights. You have just seen a negative trial that should change practice, especially given the way that we, in this country, have been prescribing ezetimibe.

Several Things to Notice About This Study and Dr Kastelein’s Presentation

It seems to be a strong study for one focusing on a surrogate outcome of artery thickness. In the Atorvastatin versus Simvastatin on Atherosclerosis Progression (ASAP) investigation, his earlier study of a similar population, such an approach showed that more intensive lipid lowering with atorvastatin was associated with less progression of atherosclerosis.4 In a pediatric population, in another Kastelein study, this approach showed that pravastatin compared with placebo was associated with less progression of atherosclerosis.4 In ENHANCE, the addition of ezetimibe to a statin did not slow the progression of atherosclerosis. This also was true for various subgroups, including those who were statin-naïve, and those who were stratified by baseline artery wall thickness.

Critics may opine about reasons for the findings, including the possibility the measures were not precise enough or the population was not typical—but the most likely explanation is that the compound did not work. It lowered LDL but did not retard the progression of atherosclerosis as we saw in prior studies in which the use of statin therapy or intensive statin therapy had this effect. This is still just one study of ezetimibe and one that used measurements of arteries and not clinical end points, but this study provides no new evidence to support the use of the drug. It moves us to more uncertainty about the benefit of the drug.

What about the presumption that knowing that a drug lowers LDL is enough to know its effect on our patients? Dr Kastelein’s presentation also has a message that is important in this respect. In his 5th slide, Dr Kastelein said that ezetimibe was known to

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From the Section of Cardiovascular Medicine and the Robert Wood Johnson Clinical Scholars Program, Department of Medicine; Section of Health Policy and Administration, School of Public Health, Yale University School of Medicine; and the Center for Outcomes Research and Evaluation, Yale-New Haven Hospital, New Haven, Conn.

Correspondence to Harlan M. Krumholz, MD, Yale University School of Medicine, 1 Church St, Suite 200, New Haven, CT 06510. E-mail harlan.krumholz@yale.edu

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reduce LDL cholesterol when added to a statin but that the effect on the progression of atherosclerosis was not known. This is a very important slide. This study was developed by experts.

Whether the incremental lowering of LDL by this drug had an effect on the progression of atherosclerosis was an open question, worthy of study. There is also the question of what effect the drug has on our patients—it is an open question, worthy of study. We do not know.

Remember that this is a new drug with a novel mechanism—first in class—we do not have outcomes studies.

One might say, but the drug lowers LDL—isn’t that a good thing? Shouldn’t that be associated with benefit? Wasn’t that enough for the Food and Drug Administration?

Although LDL is an important risk factor for cardiovascular disease, we have already refuted the assumption that just because a drug reduces LDL it must improve patient outcomes. Hormone replacement therapy reduces LDL and is not associated with cardiovascular benefit. Torcetrapib, the Pfizer drug, lowered LDL and raised high-density lipoprotein but did not improve outcomes and never made it to Food and Drug Administration approval.

Drugs are complex compounds with an array of biological effects; knowing how they affect lipids does not tell us how they affect people. This observation does not unravel the lipid hypothesis but says it may matter how we lower cholesterol. The drugs that we use make a difference in the net effect on people.

With Knowledge of Its Effect on LDL But No Information About Its Effect on the Progression of Atherosclerosis or Patient Outcomes, How Have We Used This Drug?

We in the United States have embraced this medication. Amid an aggressive marketing campaign, this drug has been rapidly adopted into practice and has become one of our favorite options for patients with hypercholesterolemia. Within 6 years of its introduction, prescriptions for Zetia and Vytorin in this country skyrocketed. In a report published online today by the New England Journal of Medicine, Jackevicius et al show that by 2006, 4 years after its introduction, 15% of US prescriptions for lipid-lowering agents included ezetimibe. In Canada, the rate was only 3%. In the United States, ezetimibe supplanted statins to some extent and led to use of lower doses of statins.

The cost was great. In 2006, we in the United States spent billions of dollars on this drug. Perhaps $1.5 to 2.0 billion more was spent than would have been had our pattern been more like the Canadians.

What Do We Know Now About the Effects of This Drug on People’s Health?

There are 3 possibilities with this drug. Eventually—one day, when outcomes studies are finally done—we may recognize that it is an effective medication for reducing cardiovascular risk. The ENHANCE study makes that less likely, but it is not impossible.

It could be that ezetimibe is simply an expensive placebo, and its principal harm is that it drains precious resources from our health care system and possibly leads people to use fewer of the drugs that have been shown to be beneficial. The ENHANCE study suggests that this may be true.

Third, it could be harmful. We do not know enough about the clinical risks of this drug. It is well tolerated and there are no obvious safety problems, but we cannot say if there is an increased risk of acute myocardial infarction or death or another important health problem.

Important clinical risks like this can be imperceptible in clinical practice; we need large clinical studies to tell us about them. We learned that with encainide and flecainide—and hormone replacement therapy—and many others.

For this novel medication for which there are some plausible biological mechanisms that could link it with harm (see the New England Journal of Medicine editorial by Taylor and Brown for some possibilities), it is important to know more about safety. No one can say with certainty that they know about the clinical risks of this drug. We just do not know. ENHANCE does not help us in this regard.

Where does this leave us? ENHANCE is an important negative study that provides no new support for a widely prescribed drug and whose surprising findings remind us how little we know about the overall risks and benefits of this drug—whether there is really a net clinical benefit to its lipid-lowering effect.

For clinicians who may have used this medication before exhausting options with statins, the strongest recommendation here is to turn back to statins, especially those with favorable outcomes data. Let us go back to what we know works. Let us stay with the evidence. Patients who need medication to treat cholesterol should be maximized on statin therapy, and different statins may need to be tried before a patient is considered to have failed statin therapy.

The next options should be medications that have been shown to be associated with better clinical outcomes: niacin, fibrates, and resins. We know that they are not tolerated as well, but they have evidence and are worth trying.

For those who have failed these therapies, and this should be a relatively small group, the question of whether we should use ezetimibe probably will be unresolved until the outcomes studies are available. Until then, we will not know the net effect of this drug on patients and whether the reduction of LDL with this drug produces a clinically meaningful effect, and
we will not really know the strategy that is in the best interests of our patients. It is an unfortunate predicament.

This study heralds the need for clinical research to guide us in decisions for our patients; ideally, this work must be done early in the drug’s development. It is not right that we are this far down the line with this drug and we have so much uncertainty about its balance of risks and benefits. We must understand the effect of new drugs on people and that relying on a drug’s effect on a set of laboratory tests may not tell the whole story. We have learned this lesson before. It appears that we must learn it again.

Since March 2008, evidence has emerged to support our message. Among many examples, trials have shown that reducing glycosylated hemoglobin below 7% does not provide additional benefit6–8; that reducing triglyceride levels in patients with diabetes does not reduce risk9; that lowering blood pressure below current guidelines for patients with diabetes does not reduce risk10; and that increasing hemoglobin levels with darbepoetin-α for patients with chronic kidney disease does not improve outcomes.11 The Institute of Medicine has published a report warning about inferring the effect of a drug or food on people based on its effect on surrogate outcomes and biomarkers.12

A focus on what the patient experiences forms the core of outcomes research13,14; the ultimate test of any intervention or policy is its effects on people.15,16 We are increasingly appreciating that drugs have many effects, and changes in single biomarkers do not always capture the full range of a drug’s impact on individuals. The net effect can only be known by studies that assess patient outcomes, including safety outcomes. In the case of ezetimibe, we are still waiting.

Disclosures

Dr Krumholz chairs a scientific advisory board for UnitedHealthCare, and is a Director of the Center for Cardiovascular Outcomes Research at Yale University, funded by the National Heart, Lung, and Blood Institute.

References

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Correction

In the Editor’s Perspective by Krumholz, “Emphasizing the Burden of Proof: The American College of Cardiology 2008 Expert Panel Comments on the ENHANCE Trial,” which appeared in the November 17, 2010 issue of the journal (Circulation: Cardiovascular Quality and Outcomes. 2010;3;565–567), the following correction is required.

In the fifth paragraph, under the heading “What Do We Know Now About the Effects of This Drug on People’s Health,” the word ‘not’ was omitted from the last sentence. The paragraph should read:

“For this novel medication for which there are some plausible biological mechanisms that could link it with harm (see the New England Journal of Medicine editorial by Taylor and Brown for some possibilities), it is important to know more about safety. No one can say with certainty that they know about the clinical risks of this drug. We just do not know. ENHANCE does not help us in this regard.”

The Editor apologizes for the error.

This correction has been made to the current online version of the article, which is available at http://circoutcomes.ahajournals.org/content/3/6/565.full.

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