James Stevermer, MD, MSPH
Associate Editor, *The Journal of Family Practice*
University of Missouri, Columbia

ENHANCE study: Ezetimibe lowers LDL, but does it matter?

We cannot be sure of clinical benefits until the ongoing trial reports the patient-oriented outcomes

FAST TRACK

I suspect that many were surprised that a markedly lower LDL level did not lead to decreased intima-media thickness

Uncertain what to advise patients whose cholesterol is not ideally controlled, even while they are taking a statin? Unfortunately, I'm afraid the recent publication of the analysis of the ENHANCE study (Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression),[1,2] did little to shed light on the question. I've been telling my patients, up front, that we do not yet know for certain whether adding ezetimibe lowers their risk of significant vascular events, even though it does lower LDL.

The ENHANCE study was a well-done randomized trial of ezetimibe 10 mg daily or placebo, along with simvastatin 80 mg daily, tested in patients with familial hypercholesterolemia. These were not your typical patients with minor lipid issues. Their average low-density lipoprotein (LDL) concentration at entry was about 318 mg/dL, with a total cholesterol of 400 mg/dL.

ENHANCE: No difference in intima-media thickness

Ezetimibe was effective in lowering LDL. At 24 months, the ezetimibe group had an LDL of 141 mg/dL, compared with 193 mg/dL in the control group. The primary outcome was carotid artery intima-media thickness (IMT). While the ezetimibe group had a slightly larger decrease in IMT than the control group, this difference was not statistically significant. (There is reasonable evidence that IMT is a marker for coronary events, but the correlation is not perfect.) I suspect many were surprised by this result—that a markedly lower LDL level did not lead to a difference in IMT, especially in this very-high-risk population.

SANDS: Combination therapy lowers IMT

At the same time, another study suggests that a multifactorial intervention, which included ezetimibe, was effective in *decreasing* IMT—at least in a population of Native Americans with diabetes.[3] The SANDS study was a randomized controlled trial of intense blood pressure and lipid management in diabetes mellitus, based on predetermined targets. The LDL target was 70 mg/dL in the intervention group and 100 mg/dL in the control group. If subjects in either group had not met their target on maximal doses of a statin, they were given ezetimibe. When appropriate, non-LDL cholesterol was treated with additional medications, such as niacin. In the end, the intervention group was taking an average of 1.5 cholesterol drugs vs 1.2 for the control group. The authors did not report which medications patients were taking at the end of the trial. Because the intervention included tighter blood pressure control as well, it's not surprising to note that the intervention

group was taking more antihypertensive medications, as well (2.3 vs 1.6 for the control group).

Carotid intimal thickness decreased in the intervention group and increased in the control group ($P<.01$), but the study was underpowered to find a difference in clinical outcomes. Secondary analysis suggested the IMT difference was primarily due to the lipid intervention, but this finding is by no means certain.

Controversy about use of intermediate markers

The issue of intermediate markers is particularly complicated in the treatment of cholesterol. Although the evidence is clear and incontrovertible that statins reduce coronary artery events, there remains legitimate controversy about the setting of LDL targets, especially below 130 mg/dL.[4] The SANDS trial is one of the first to compare results of using differing LDL targets, but it sheds only a little light on this question, as it reported only intermediate targets, and blood pressure control was also better in the intervention group.

Should disease-oriented evidence change practice?

In general, I hesitate to recommend changing practice solely based on disease-oriented evidence, such as LDL levels. And this situation is particularly challenging. Here, we have an intervention (use of ezetimibe) widely adopted into practice without evidence of clinical benefit, because it clearly lowers LDL levels. A troubling fact: Since its introduction, ezetimibe, prescribed either by itself (Zetia) or in a formulation combined with simvastatin (Vytorin), has had rapid market share growth, some of which appears to have been in place of statins. Rates of statin use in the United States, equal to those in Canada in 2002, have not kept up with increases in Canada, while ezetimibe has risen to about 15% of all lipid-lowering agent prescriptions, a much higher rate than in Canada, as of 2006.[5] In 2006, the US expenditure on ezetimibe was $2.7 billion.

In the ENHANCE study, this drug did not reduce an intermediate marker (IMT) in a very-high-risk population, yet we don't really know if IMT is a better predictor of patient outcomes than LDL cholesterol level. And it's certainly arguable that neither improvement is great enough to warrant billions of dollars annually.

Be up front with patients

What am I going to do in the office tomorrow? Just as there aren't data to suggest we should stop the use of ezetimibe in a wholesale fashion, there aren't data to support its widespread use in a wholesale fashion. I can't get enthusiastic about prescribing ezetimibe for most patients.

What about patients' questions? I think we need to tell them that their expensive medicine lowers their LDL, but we have no idea if it prevents any of the outcomes that we really care about.

We'll know more when the ongoing trial based on patient-oriented outcomes is reported, but that's still a ways off (and an editorial topic for another day). ■

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Direct editorial information and inquiries to:

EDITORIAL OFFICE
Health Professions Building, Department of Family Medicine, PO Box 670582, Cincinnati, OH 45267-0582
Telephone: (513) 558-4021

PUBLISHING OFFICES
Dowden Health Media, Inc, 110 Summit Avenue, Montvale, NJ 07645
Telephone: (201) 740-6193
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