In this issue of the Journal, Kastelein et al.\(^1\) report the results of a 2-year study comparing daily therapy with 80 mg of simvastatin plus either placebo or 10 mg of ezetimibe on the average change in carotid intima–media thickness in patients with familial hypercholesterolemia. The study, called the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial, showed no significant between-group differences in any of several end points with respect to intima–media thickness (a commonly used risk surrogate for vascular disease) or clinical results, despite a between-group difference in levels of low-density lipoprotein (LDL) cholesterol of 51 mg per deciliter (1.32 mmol per liter).

This seemingly rigorous and well-executed study of a combination therapy that has been approved by the Food and Drug Administration dramatically contradicts our expectations. “Lower is better” has been the mantra with respect to LDL cholesterol for the past two decades. During a period of 3 to 6 years, most controlled trials of statins, resins, or partial ileal bypass have shown clinical or imaging benefits that correlated with the concurrent reduction in LDL cholesterol.\(^2\)

A seemingly perfect analogue of the ENHANCE trial, the Atorvastatin versus Simvastatin on Atherosclerosis Progression (ASAP) trial,\(^3\) compared daily therapy with 80 mg of atorvastatin with therapy with 40 mg of simvastatin in 325 patients with familial hypercholesterolemia. The patients in the two studies were virtually identical in age (48 years) and in baseline levels of both LDL cholesterol (315 mg per deciliter [8.15 mmol per liter]) and high-density lipoprotein (HDL) cholesterol (46 mg per deciliter [1.19 mmol per liter]). The two studies also used nearly identical methods for measuring carotid-artery intima–media thickness, with measurements performed in the same central laboratory. In the control groups of the two trials, the in-treatment level of LDL cholesterol was 193 mg per deciliter (4.99 mmol per liter) among patients receiving 80 mg of simvastatin in the ENHANCE trial and 186 mg per deciliter (4.81 mmol per liter) among those receiving 40 mg of simvastatin in the ASAP trial. At 2 years, the increases in carotid-artery intima–media thickness were 0.0058 mm in the ENHANCE trial and 0.036 mm in the ASAP study.

However, the intensive-therapy groups in the two studies differed in their responses. Among patients in the ENHANCE study who had an LDL cholesterol level of 178 mg per deciliter (4.60 mmol per liter) while receiving combination therapy with simvastatin plus ezetimibe, the carotid intima–media thickness progressed by 0.0111 mm. With a similar level of LDL cholesterol (167 mg per deciliter [4.32 mmol per liter]) during therapy with 80 mg of atorvastatin in the ASAP study, intima–media thickness regressed substantially, by 0.031 mm. Three differences between the two trials might explain this substantial discrepancy: First, the baseline intima–media thickness was 0.695 mm in the ENHANCE study, as
compared with 0.925 mm in the ASAP study. Second, patients in the ENHANCE study almost certainly had a longer and more intensive history of statin therapy than did those entering the ASAP study 6 years earlier. And third, the intensive-therapy group in the ENHANCE study received ezetimibe, whereas the corresponding group in the ASAP study did not.

Should we conclude from the ENHANCE study that the addition of ezetimibe to a high-dose statin is very effective in lowering LDL cholesterol but has no added value in the all-important arenas of atherosclerosis and (presumably) clinical benefits? Before concluding so, we must address the following four questions:

First, is the rate of change in carotid intima–media thickness an effective surrogate for the rate of cardiovascular clinical events? Among 34 studies of the correlation between intima–media thickness and angiographic evidence of coronary atherosclerosis, 30 have shown a modest positive relationship, similar to that found in autopsy studies. One study that involved 8.8 years of follow-up without therapy found that an annual increase of 0.03 mm in intima–media thickness was associated with a tripling of the rate of coronary events. The measurement of intima–media thickness has been the focus of at least 15 lipid-therapy trials. Among seven studies comparing various statins (drugs known to reduce coronary events) with placebo or with lower-dose statins, the progression of intima–media thickness has consistently been slowed or has even regressed with higher doses of statins. However, no study with 2 years or less of follow-up has shown a significant reduction in such events. This result is probably because 1 to 2 years are required for lipid depletion to stabilize plaque before clinical benefits emerge. In three trials, drugs from two new classes were added to statins, resulting in a substantial incremental, favorable effect on lipids, even though there was a small trend toward increased coronary events and there was no between-group difference in the primary end point of carotid intima–media thickness. Thus, although a reduction in intima–media thickness does not guarantee a reduction in the rate of events, it seems unlikely that a reduction in events can be expected without a reduction in the progression of intima–media thickness. The ENHANCE trial was not powered to show an effect on event rate attributable to ezetimibe, but since the progression of intima–media thickness was not slowed in 2 years, no effect on events would be expected in this specific population, even with prolonged treatment.

Second, how important is statin pretreatment? Most 45-year-old patients with familial hypercholesterolemia have received statins, resins, ezetimibe, or various combinations of these agents, with increasing intensity as treatments have evolved, for one or two decades. If long-term therapy before entering a trial favorably alters the plaque, the potential for showing a benefit of treatment would be diminished in such patients. Large plaque lipid pools and increased density of macrophage foam cells are highly predictive of the likelihood and location of atherothrombotic rupture in fatal myocardial infarction. The emerging hypothesis is that lipid therapy depletes plaque lipids, resulting in plaque stability and clinical quiescence. In the ENHANCE study, the mean baseline measure of carotid intima–media thickness was 0.70 mm, which is much thinner than that in the ASAP study and also thinner than expected. This finding supports the hypothesis that previous plaque lipid depletion is an explanation for the results of the ENHANCE study. The argument against this hypothesis is that, among the 19% of patients who were not receiving statins at the time of study enrollment, those who were treated with the combined regimen of simvastatin plus ezetimibe did not have a better response than did those receiving simvastatin alone. More detailed pretreatment history is needed for such patients.

Third, does the absence of between-group differences in HDL cholesterol and triglycerides make any difference? Possibly. Although most all trials of the lowering of LDL cholesterol have had small favorable effects on HDL cholesterol, triglycerides, and sometimes lipoprotein(a), the observed benefits have generally been attributed to the lowering of LDL cholesterol. However, if these small changes in other lipid measures have greater-than-proportional benefits, then the absence of ezetimibe-related benefits of HDL cholesterol and triglycerides may be important. Such changes fall into the general category of pleiotropic effects of statins that include reduced vascular and platelet reactivity. In scattered small studies, these biomarkers appeared to be less favorably affected by ezetimibe than by statins. Ezetimibe diminishes intestinal cholesterol ab-
sorption by inhibiting the Niemann–Pick C1-like 1 (NPC1L1) enterocyte receptor, but it may trigger other proatherogenic gene-regulatory mechanisms, including the inhibition of scavenger receptor B1 (SR-B1) and ATP-binding cassette transporter A1 (ABCA1). These effects are perhaps not relevant here, since ezetimibe is only fractionally absorbed systemically. Nevertheless, it is important to remember that the unfocused inhibition or promotion of gene expression can have unintended consequences.

Fourth, does the ENHANCE study prove that ezetimibe provides no benefit when added to statin therapy or, for that matter, as monotherapy? That possibility, which is the elephant in the parlor, deserves serious consideration in any discussion of the results of this study. Further answers to these questions, as well as results of trials that are under way,13,16 will clarify the findings of the ENHANCE study, which, after all, are based on a surrogate, although seemingly useful, end point. For now, the study’s findings are a red flag but not a black box. The lack of benefit in the reduction of carotid plaque may be explained by the above-mentioned mechanisms, particularly by previous plaque lipid depletion, in which case a similar but longer trial in patients who have not undergone previous therapy could well show the anticipated clinical benefit of ezetimibe. Alternatively, these findings plus future biologic and clinical evidence could confirm that the benefits of lowering LDL cholesterol may depend not only on “how low you go” but also on “how you get there.”

In the meantime, the thoughtful clinician may elect to adopt the following reasonably cautious strategy, which is similar to that recommended in the January 15 statement of the American College of Cardiology17: First, achieve targets for levels of LDL and HDL cholesterol (or of the ratio of total cholesterol to HDL cholesterol) with the use of statins plus drugs that have shown clinical benefits when added to statins (e.g., nicotinic acid, fibrates, and bile acid sequestrants), as tolerated. Second, use ezetimibe in patients who, despite the above-mentioned therapy, do not achieve their individual targets. And third, wait for clarifying studies.

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