After much speculation, to the point of congressional involvement, regarding the reasons for the delay in reporting the results of a relatively small trial of carotid-artery imaging in patients with familial hypercholesterolemia (FH), a brief top-line synopsis was released this year on January 14 (1). The study, called ENHANCE (Effect of Combination Ezetimibe and High-Dose Simvastatin versus Simvastatin Alone on the Atherosclerotic Process in Patients with Heterozygous Familial Hypercholesterolemia), was designed to determine if an anticipated additional reduction in LDL-cholesterol (LDLc) of 18% when ezetimibe 10 mg was added to 80 mg of simvastatin (Vytorin 10/80 mg) versus 80 mg simvastatin alone would result in either less progression or more regression of carotid atherosclerosis as measured by intima-media thickening (cIMT). The study was conducted over a 2-year period and enrolled 720 FH patients, with roughly equal numbers of men and women, mean age 45 years. Although patients had very high LDLc concentrations of nearly 320 mg/dL (8.32 mmol/L) after all lipid-lowering agents were washed out, more than 80% had been on prior statin treatment, including high-dose treatment, for many years before entry into the trial. The changes in cIMT after 2 years did not significantly differ from baseline for either treatment group or from one treatment group to the other. The popular press contacted selected “experts” who gave flamboyant, misleading, and sometimes self-serving or agenda-driven comments (2) interpreting the results either as a failure of the mechanism by which LDLc was decreased, or as evidence that LDLc reduction itself was not an effective way to ameliorate the course of atherosclerosis. The complete details of ENHANCE have now been published (3), and a more complete evaluation is possible. A number of critical flaws in the trial are apparent.

The second critical factor for demonstrating the superiority of one treatment to another is that one of the treatment groups must show a statistically significant worsening or improvement compared to the other group in the variable selected for measurement as a disease indicator (in this case the cIMT). ENHANCE was designed to have a power of 90% to detect a difference of 0.05 mm in cIMT between groups within the 2 year trial period. In ASAP, the study on which ENHANCE was based, the progression in cIMT during the 2-year trial period in the simvastatin 40-mg treatment group (expected LDLc decrease 40%) was 0.036 mm. At the end of the 2-year ENHANCE trial the change in cIMT was substantially less than projected in both groups, 0.011 mm in the Vytorin group and
0.005 mm in the simvastatin 80-mg group ($P = 0.29$, not significant). No matter what segment of the carotid artery or the femoral artery was examined, there was no change from baseline during the 2-year trial period and no difference between the treatment groups. Thus, considering both trials, done 5 years apart, a 40% reduction in LDLc, with the same drug in the same patient population and similar entry LDLc concentrations resulted in 3–7-fold less progression of cIMT in ENHANCE. The only difference between the 2 studies in the simvastatin monotherapy groups was the pretreatment of patients and the amount of baseline atherosclerosis in ENHANCE.

What about the comments in the popular press by Nissen, Topol, and others? (2, 4). Is there merit to the statements that either the mechanism by which ezetimibe works does not impact atherosclerosis (in this case a surrogate indicator measured by ultrasound), or worse still that the entire LDL hypothesis is flawed and the antiatherosclerotic benefits seen with LDLc-lowering drugs are attributable only to statins and are due to pleotropic effects manifested via their antiinflammatory action, as exemplified by a biomarker such as high-sensitivity C-reactive protein (hs-CRP)? Let’s review these statements in turn.

(a) The mechanism by which ezetimibe lowers LDLc is not antiatherosclerotic. This comment appears to have been made by someone who lacks any understanding of basic lipid metabolism. The final pathway by which circulating LDLc concentrations are decreased with statins, bile acid sequestrants, and cholesterol absorption inhibitors is identical and occurs via upregulation of the LDL receptor secondary to intracellular cholesterol depletion. Certainly statins do this better than any other class of agents, which makes it easier to show decreases in atherosclerosis by assessment of both clinical events and surrogate measurements like cIMT, particularly when the control group is treated with placebo. It is much more difficult, however, to show the benefit of smaller increments in LDLc reduction, such as between patients receiving different doses of the same statin, or different statins. For example, it took more than 5 years for the TNT (Treat to New Targets) study of $>10000$ high-risk patients with coronary artery disease (CAD) to show that the additional 18% reduction in LDLc with 80-mg atorvastatin was a superior result compared to that seen in patients taking 10 mg of the same drug. In the IDEAL (Incremental Decrease in End Points Through Aggressive Lipid Lowering) trial, when only a 12%–14% LDLc difference was assessed with the use of 80 mg of atorvastatin versus 20–40 mg of simvastatin in 8888 CAD patients, the study failed on its primary endpoint, although it achieved numerous secondary endpoints. Another large trial, which includes 10 000 CAD patients, SEARCH (Study of the Effectiveness of Additional Reduction in Cholesterol and Homocysteine), is comparing simvastatin doses of 20 mg versus 80 mg and has shown an LDLc difference of about 12% and is still in progress after 7 years, 3 years later than projected completion. In addition, at least 3 trials with bile acid sequestration have demonstrated reduction in cardiovascular disease events, the POSCH (Partial Ileal Bypass Surgery), Lipid Research Clinics–Coronary Primary Prevention Trial, and Colestipol Trial. In fact, the first 2 National Cholesterol Education Program–Adult Treatment Panel guidelines were published before completion of any clinical end-point trials with statins and were based primarily on the ability of bile acid sequestration to reduce CAD events.

(b) The LDLc hypothesis is flawed, and it is the “pleotropic” effect of statins that reduces inflammation and thereby favorably impacts atherosclerosis. This hypothesis relies mostly on the faith placed in the inflammatory marker hs-CRP, attributable mainly to epidemiological data and the changes seen in a number of statin trials, in which changes in hs-CRP appeared to be a better predictor of risk reduction than decreases in LDLc. The observation that little if any decrease in hs-CRP occurs with ezetimibe monotherapy has led some to question whether the antiatherosclerotic effects of this treatment are similar to those of LDL-lowering equivalent doses of statins. When ezetimibe is added to statins, however, there is a large and robust incremental decrease in hs-CRP. In the ENHANCE trial, the decrease in median hs-CRP associated with the addition of ezetimibe to simvastatin was almost 27%, more than double the effect of statin alone (23.5% versus 49.2%, $P < 0.01$)! Thus if ENHANCE brings the LDLc hypothesis into question it surely does as much, if not more, to cast doubt on the role of inflammation in atherosclerosis as determined by hs-CRP.

In summary the “failure” of the ENHANCE trial to show a treatment benefit with the addition of ezetimibe to simvastatin appears to be more one of patient selection and design than treatment. As has been the case for other trials demonstrating the benefits of other relatively modest differences in LDLc reduction between therapies, such as TNT and IDEAL, conclusive evidence showing the benefits, or lack thereof, of ezetimibe when added to statin therapy must be obtained from clinical endpoint data from much larger and longer trials in high-risk CAD patients. These trials, involving nearly 20 000 patients in 2 studies, SHARP (Study of Heart and Renal Protection) and IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial), are underway and will evaluate the risk reduction provided by Vytorin 10/40 mg compared to simvastatin (Zocor) 40 mg in reducing death and major coronary events.
Results of these trials are anticipated to be available in 2 to 3 years.

ENHANCE also has implications for future trials of LDLc-decreasing or HDLc-increasing agents that use either cIMT or coronary intravascular ultrasound. It now becomes critical to select the population extremely carefully, to understand which assumptions from prior trials may no longer apply, and to likely increase both the number of patients per group and the duration of treatment.

Finally, although the ENHANCE trial results have been less than optimal for the sponsors of the trial, the outcome actually provides very good news for those with FH, and all patients on long-term lipid-lowering therapy, in that the data seem to strongly indicate that treatments that bring about moderate, long-term LDLc decreases dramatically reduce the atherosclerotic burden, at least in carotid arteries, and virtually halt progression of the underlying disease. Thus the glass is not half empty but is clearly more than half full!

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