CORRESPONDENCE

Simvastatin with or without Ezetimibe in Familial Hypercholesterolemia

TO THE EDITOR: In the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) study by Kastelein et al. (April 3 issue),[1] the addition of ezetimibe to simvastatin boosted the decrease in levels of low-density lipoprotein (LDL) cholesterol from 39.1% to 55.6%. However, the greater decrease in LDL cholesterol in the combined-therapy group did not affect progression of the carotid intima–media thickness. Some observers have suggested that the results of the ENHANCE study force us to question the basic lipid hypothesis of atherogenesis.

No single study can possibly counter the extensive body of evidence that lowering of plasma cholesterol levels decreases the risk of coronary heart disease. As pointed out by the investigators in the Coronary Primary Prevention Trial, a reduction in risk in the pre-1984 outcome trials correlated well with the decrease in plasma cholesterol levels, whether that change was effected by means of diet, nicotinic acid, or cholestyramine.[2] The statin results fit rather well on the same straight line.[3] In short, the prevention of coronary heart disease depends primarily on a reduction in LDL cholesterol, independently of the mechanism of LDL lowering. One negative study is surely not a sufficient basis for challenging the lipid hypothesis, especially since a number of factors could have readily accounted for the apparent negative result in patients receiving ezetimibe, as pointed out in the commentaries accompanying the article.[4,5]

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TO THE EDITOR: Given the extremely high cholesterol levels reported in the ENHANCE study, the results of this trial are not applicable to the general population and do not represent changes in plaque that might have been seen in patients with less severe hyperlipidemia. Although there is some

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relationship between a change in the intima–media thickness and a reduction in cardiac events,[1] other mechanisms are important, such as plaque stabilization and reduction in inflammation.

The results of multiple statin trials have shown a consistent association between levels of LDL cholesterol and C-reactive protein (CRP) and clinical events.[2,3] In the ENHANCE trial, levels of LDL cholesterol and CRP were lower in the combined-therapy group than in the simvastatin-only group, which suggests that event rates are likely to be lower when the clinical outcome trials are completed.

The media has created an undue panic in the general population on the basis of a study that offers little insight into the benefits or dangers of combination therapy with simvastatin and ezetimibe. Other drugs have had surrogate measures that at first appeared to be adverse. Had we never used beta-blockers to treat heart failure because they initially reduce the ejection fraction,[4] we would have denied many patients a lifesaving therapy.

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TO THE EDITOR: The results of the ENHANCE study, which involved patients with familial hypercholesterolemia, are at first glance perplexing. Greater lowering of LDL cholesterol levels after 2 years of treatment did not improve the intima–media thickness of the carotid and femoral arteries. However, atherosclerotic blockages in 45-year-old men change very slowly, as indicated in a study of cholesterol turnover in human atherosclerotic arteries.[1] The turnover time of cholesterol was 821 and 934 days in the femoral and carotid arteries, respectively. One would not expect to see much change in the arteries of these study patients after only 730 days.

In their accompanying editorial, Brown and Taylor suggest an additional factor. The patients in the study had already been treated with statin drugs for years. Most likely, the benefit had already occurred with the loss of lipids from atherosclerotic plaques. The resultant fibrotic, calcified lesions would not be expected to change very much as levels of LDL cholesterol were further lowered. It is reassuring that the safety of ezetimibe was demonstrated in these 338 patients and that ezetimibe also reduced the CRP level significantly.

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TO THE EDITOR: Kastelein et al. defend the precision of their carotid ultrasonographic methodology on the basis of its "high intraclass correlation coefficient and . . . small standard deviations." Although this precision is sufficient for measurements of intima–media thickness of approximately 700 μm, as reported by the authors, the relative errors become substantially magnified for the much smaller derived differences representing the operative primary outcome. According to our calculations, the difference in the mean (±SD) carotid intima–media thickness was 6±66 μm in the simvastatin-only group, as compared with 11±68 μm in the group receiving simvastatin plus ezetimibe. These large errors become magnified even further for the resultant between-group differences — averaging $(11–6)\pm\sqrt{(66^2+68^2)}$, or 5±95 μm (less than the width of a red cell), with a 95% confidence interval ranging from –181 to 192 μm (the width of more than 50 red cells). These tiny differences and large errors provide no information whatsoever for or against the study hypothesis or any of its putative corollaries. Nor do they say anything about the likely denouement of ongoing clinical-outcome studies. Simply stated, the absence of evidence is not evidence of absence.

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Dr. Diamond reports being a former employee of Merck (1995 to 1996) and receiving lecture fees from Merck and Schering-Plough. No other potential conflict of interest relevant to this letter was reported.

TO THE EDITOR: In their editorial, Brown and Taylor do not consider imaging methodology as a factor in the results of the ENHANCE trial. Carotid–intima thickening suffers from a lack of consensus on measurement technique.[1] Different techniques have a large effect on reproducibility, and error contributes significantly to observed changes in longitudinal studies.[1] Reproducibility is greater for the distal common carotid artery than for the bulb or internal carotid.[1,2] Accordingly, the common carotid artery alone has been studied in most major trials other than the ENHANCE and the Atorvastatin versus Simvastatin on Atherosclerosis Progression (ASAP) studies, including a trial cited by Brown and Taylor and by Kastelein et al., which showed a correlation between an increase in the intima–media thickness and a tripling of the cardiovascular risk.[1-3]

Since subjects in the ASAP study had grossly abnormal intimal thickening with "visible plaque," the methodology was less critical in detecting regression.[4] However, in the ENHANCE study, among healthy subjects in the simvastatin-only group who had progression in the intima–media thickness of only 0.0058 mm at 2 years, the inclusion of the carotid bulb and the internal carotid artery produced a standard deviation between paired quality-control measurements of 0.056 mm, which limits the statistical power of the study. Notably, confining the analysis to the common carotid artery actually shows a trend in favor of ezetimibe. Although it emphasizes the primary role of statins, the study is too limited to remove ezetimibe as an important adjunct.

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TO THE EDITOR: The editorial by Brown and Taylor addressing the ENHANCE trial suggests that ezetimibe may trigger proatherogenic gene-regulatory mechanisms. The basis for this claim comes from an in vitro study involving Caco-2 (colon carcinoma cell line), in which crushed ezetimibe pills (10% ezetimibe and 90% non-ezetimibe formulation) caused the inhibition or gene downregulation of scavenger receptor B1 and ATP-binding cassette transporter A1. In contrast, numerous studies of tissues derived from ezetimibe-treated animals have shown no effect on the expression of these genes.[1-3] Studies of ezetimibe in a variety of species and in mice with a deletion of its molecular target, the Niemann–Pick C1-like 1 (NPC1L1) enterocyte transporter, have consistently shown selective inhibition of cholesterol uptake from the intestine,[3] without showing off-target effects. Changes in gene expression reflect this inhibition — for example, increased expression of genes encoding the LDL receptor and cholesterol biosynthesis. In animal models, ezetimibe treatment caused an inhibition of atherosclerosis of more than 90%[3] and extended lifespan.[4] The deletion of NPC1L1 in apolipoprotein E–null mice causes nearly complete protection from atherogenesis.[5] The data strongly support an antiatherogenic role of ezetimibe through its selective inhibition of NPC1L1-mediated intestinal absorption of cholesterol.

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TO THE EDITOR: Brown and Taylor recommend using drugs that have shown clinical benefits when added to statins before using ezetimibe with statins. They reference studies demonstrating the clin-

ical benefit of adding niacin to statins, but I am unaware of any study that shows a clinical benefit of adding fibrates or bile acid sequestrants to statins. Fibrates, bile acid sequestrants, and ezetimibe should be reserved for patients in whom individual lipid targets have not been reached with a statin and niacin or who do not tolerate this combination. One should choose among these three agents on the basis of efficacy, potential drug–drug interactions, side effects, and cost.

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Dr. Kaye reports receiving lecture fees from Merck–Schering-Plough. No other potential conflict of interest relevant to this letter was reported.

THE AUTHORS REPLY: For several decades, the lipid hypothesis has been universally accepted. Randomized, controlled trials with statins, resins, or even partial ileal bypass have shown that reductions in LDL cholesterol levels are accompanied by a clinical benefit as well as improvement in atherosclerosis, as assessed with imaging techniques.[1,2] We share Steinberg's position that a small surrogate-marker trial such as ours does not carry the weight to challenge this hypothesis.[3] Furthermore, Eichhorn states that in multiple statin trials, levels of LDL cholesterol and CRP were lowered in a manner similar to that in our study. It is not far-fetched to expect that ezetimibe, like statins, might ultimately also reduce cardiovascular events in outcome trials, but this is by no means a certainty, given the results of our study. The unanticipated results of our study could be caused by the extent of previous lipid-lowering treatment, the imprecision of ultrasonographic techniques, the short duration of treatment, or off-target effects of ezetimibe that offset the reduction in LDL cholesterol. A final conclusion must await the results of the ezetimibe clinical-end-point study.

Connor points to the aggressive lipid-lowering treatment and the ensuing "delipidation" of the arterial wall as a major reason that our trial did not show an effect of the addition of ezetimibe, and he might well be right. However, he also mentions "atherosclerotic blockages" and "atherosclerotic plaques." Although this may be a mechanism in patients with more severe disease, in our trial, no patients had extensive carotid atherosclerosis: only 24 of 642 patients (3.7%) had small plaques (defined as an intima–media thickness ≥1.3 mm) in one or more of their carotid segments. As in many other trials studying carotid intima–media thickness, most of the data from our study represent overall thickening, the stage that precedes plaque formation.

Diamond and Kaul state that "the absence of evidence is not evidence of absence," and if they mean that our results cannot be interpreted as proof that ezetimibe has no clinical benefit, we agree. However, if their contention is that with respect to the primary efficacy outcome a beneficial treatment effect of ezetimibe could be "hidden" because of what they call tiny differences and large errors, we strongly disagree. It is obvious that the standard deviations for the measurement of intima–media thickness are higher than the actually measured differences.[4] For this reason, a large study population is needed for trials studying intima–media thickness. Our study was underpowered to detect significant differences in intima–media thickness in the range of 6 to 11 μm. On the basis of the post hoc power calculation, we could measure significant differences of only 15 μm. Despite this much-better-than-anticipated precision, no treatment effect of ezetimibe could be observed.

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THE EDITORIALIST REPLIES: Connor proposes that substantial changes in carotid intima–media thickness would be unlikely in 2 years. However, thinning has occurred with intensive statin therapy. In 2001, in the ASAP trial, and in 2003,[1] patients in these studies who received 80 mg of atorvastatin

or 80 mg of simvastatin during a 2-year period had a reduction in carotid intima–media thickness of 31 μm and 53 μm, respectively. But in 2007, in the Rating Atherosclerotic Disease Change by Imaging with a New CETP [Cholesteryl Ester Transfer Protein] Inhibitor (RADIANCE 1) trial and in 2008, in the ENHANCE trial, in which identical drugs were used in the same laboratory, patients in the same clinical population had minimal intima–media thickening (an increase of 5 μm and 6 μm, respectively) during a 2-year period. These findings had nothing to do with ezetimibe; rather, they reflect a fundamental change in the laboratory or in its patients. This newly observed lack of response to intensive statin therapy appears to be best explained by the observation that lipid-lowering therapy primarily depletes core lipid deposits and lipid-rich macrophages[2] but not elastin, collagen, smooth muscle, or calcium.[2,3] In the ENHANCE study, 81% of patients had received standard-of-care statins for many years in the expert centers that enrolled patients with familial hypercholesterolemia in this trial. In the remaining 19% of patients, the treatment history was unknown. A decade of intensive lipid therapy literally depletes the human carotid plaque of lipid.[3] Thus, these patients, having undergone long, effective treatment, were probably lipid depleted and could not respond with further intimal thinning and were similarly depleted of macrophage-derived inflammatory or growth factors, thus remaining in a quiescent progression mode.

Blake points out that different segments of the carotid bifurcation have different variances in measurement. And Diamond (with whom I would never argue about statistics) and Kaul interpret the large variance in the change in carotid intima–media thickness (e.g., 6±66 μm) as an "error" in measurement. I view this variance as largely a population variance. Nevertheless, the thin baseline carotid intima–media thickness and the absence of significant between-group differences in carotid intima–media thickness, on the basis of seven averaging approaches, convince me that the observed absence of intimal response to either of the treatments is entirely credible. The ENHANCE study neither rules out nor establishes a clinical benefit of ezetimibe in a population that has not undergone previous therapy.

Kaye requests evidence that fibrates or resins add to risk reduction with statins. He points out that there are no trials of fibrates plus statins, although the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study[4] is seen by many as showing a strong favorable trend. The benefits of lovastatin plus colestipol in the Familial Atherosclerosis Treatment Study (FATS) far exceeded the established expectations for lovastatin alone.[5]

Davis and colleagues make a number of salient and supportive points regarding cell and tissue models of the action of ezetimibe. The model of choice is the human clinical model. We await its evidence.

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Home Automated Defibrillators after Myocardial Infarction

TO THE EDITOR: In the Home Automated External Defibrillator Trial (HAT) (April 24 issue),[1] Bardy et al. recruited patients who had had a previous myocardial infarction and who were not eligible for an implantable cardioverter–defibrillator (ICD),[2] at a median interval of 1.7 years after myocardial infarction. It has been demonstrated that the absolute risk of a fatal arrhythmic event after myocardial infarction is greatest within the weeks immediately after the event and declines significantly thereafter, reaching a steady state at approximately 1 year.[3] In the study by Hohnloser et