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Cholesterol Lowering and Ezetimibe

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In this issue of the *Journal*, we publish the results of the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial,¹ which addresses the question of whether additional lowering of low-density lipoprotein (LDL) cholesterol with ezetimibe beyond the level achieved with simvastatin beneficially affects the progression of atherosclerosis. As a surrogate clinical marker for such progression, the study used imaging of the intima-media thickness of the carotid and femoral arteries. In contrast to statins, which lower LDL cholesterol by increasing its clearance, ezetimibe selectively inhibits the absorption of cholesterol by binding to Niemann-Pick C1-like 1 (NPC1L1) protein, which is involved in cholesterol processing. When administered in combination, ezetimibe and a statin lower plasma LDL cholesterol below the level that can be achieved with a statin alone.

The ENHANCE trial was conducted in patients with familial hypercholesterolemia, a condition characterized by high levels of LDL cholesterol. Patients were randomly assigned to receive either simvastatin alone or a combination of simvastatin plus ezetimibe. Combination therapy resulted in LDL cholesterol levels that were 27% lower than those achieved with monotherapy, and C-reactive protein levels were also significantly lower with combination therapy. Unexpectedly, however, the trial showed that despite increased lowering of LDL cholesterol in the group that received ezetimibe, the rate of progression of atherosclerotic disease, as measured by intima-media thickness, was the same in the two study groups. It is this paradox, which is at odds with our traditional understanding of the relationship between LDL cholesterol and atherosclerosis, that has puzzled investigators and clinicians alike. The paradox and other impor-

tant questions that are raised by the trial, including the rationale for the use of carotid intima-media thickness as a surrogate end point, are discussed in detail by Brown and Taylor in an accompanying editorial.²

Even before its publication in the *Journal*, the ENHANCE trial was the subject of intense media scrutiny and congressional inquiry. In response to this unusual level of public attention, the manufacturers of the combination drug held a news conference and released some of the data from the trial on January 14, 2008. A complete copy of the data set was provided to the academic principal investigator, who with his colleagues undertook an independent analysis of the primary data. It is this independent analysis that appears in this issue of the *Journal*. Given the high public visibility and scientific importance of the ENHANCE trial, as well as the widespread use of ezetimibe (with 34 million prescriptions written in the United States in 2006 alone, as described in detail by Jackevicius et al.³ in another article in the *Journal*), we believed that it was especially important to publish a rigorously peer-reviewed independent analysis, accompanied by expert editorial commentary. Only with the full data set and an independent analysis on the scientific record is it possible to properly interpret the trial and formulate follow-up studies to further pursue the intriguing but puzzling results. The findings, along with the observations of Jackevicius et al.,³ underscore the importance of timely reporting of the results of clinical trials such as the ENHANCE study.

As noted by Brown and Taylor, the data from this trial, which are based on measurements of intima-media thickness in lieu of clinical end points, do not directly address the question of whether the lowering of LDL cholesterol with

ezetimibe is clinically beneficial. The results of ongoing trials, such as NCT00202878 (also known as Improved Reduction of Outcomes: Vytorin Efficacy International Trial [IMPROVE-IT]), which will not be available until at least 2011, are expected not only to help define the role of ezetimibe in the treatment of hypercholesterolemia but also to provide insight into the biology of LDL cholesterol lowering and the use of carotid intima-media thickness as a surrogate indicator of coronary events.

Until such data are available, it seems prudent to encourage patients whose LDL cholesterol levels remain elevated despite treatment with an optimal dose of a statin to redouble their efforts

at dietary control and regular exercise. Niacin, fibrates, and resins should be considered when diet, exercise, and a statin have failed to achieve the target, with ezetimibe reserved for patients who cannot tolerate these agents.

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