

For years, physicians have used ezetimibe to lower cardiac risk in patients with hypercholesterolemia, either as a single product (Zetia) or in combination with simvastatin/Zocor (as Vytorin). Ezetimibe was originally approved by the FDA solely on the basis of its capacity to lower LDL cholesterol; unlike many statins, it has not been shown to reduce the risk of cardiac events.

The ENHANCE trial¹ was designed to determine whether ezetimibe in combination with simvastatin might improve the cardioprotective effects of statin therapy alone. Nearly two years passed between completion of this industry-funded study and release of its initial results.

ENHANCE enrolled 720 patients with heterozygous familial hypercholesterolemia with baseline LDL cholesterol levels of approximately 318 mg/dL to receive combination ezetimibe + high-dose simvastatin (Vytorin), or simvastatin alone. In addition to cholesterol levels, the study measured the thickness of the arterial intima over a 24-month period. The study found that although the combination product lowered LDL more than a statin alone (141 mg/dL v. 193 mg/dL), this was not accompanied by an advantage in the level of atherosclerosis.²

Thus, while ezetimibe (alone or in combination with simvastatin) has been shown to lower LDL, there is no reliable data that it reduces the risk of cardiovascular events. Without this information, it is not clear that either Zetia or Vytorin offers a clinical advantage over simply optimizing dosages of well tested and proved statins.

While waiting for further data, what should clinicians do? First, clinical efforts should be directed at getting the patients' LDL down to target levels using a statin alone. Second, if an additional agent is needed, add another drug that has been shown to have clinical benefits when added to statin therapy (e.g., nicotinic acid, fibrates, and bile acid sequestrants).³ Finally, use ezetimibe for the rare patient who cannot tolerate statins or cannot get to their LDL goal despite these steps.

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¹ Kastelein JJ, et al. Comparison of ezetimibe plus simvastatin versus simvastatin monotherapy on atherosclerosis progression in familial hypercholesterolemia. Design and rationale of the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial. *Am Heart J.* 2005;149:234-9.

² Kastelein, JJ, et al. Simvastatin with or without ezetimibe in familial hypercholesterolemia. *NEJM* 2008;358(14):1431-43.

³ Brown, G, Taylor, AJ. Does ENHANCE diminish confidence in lowering LDL or in ezetimibe? *NEJM* 2008;358(14):1504-7.