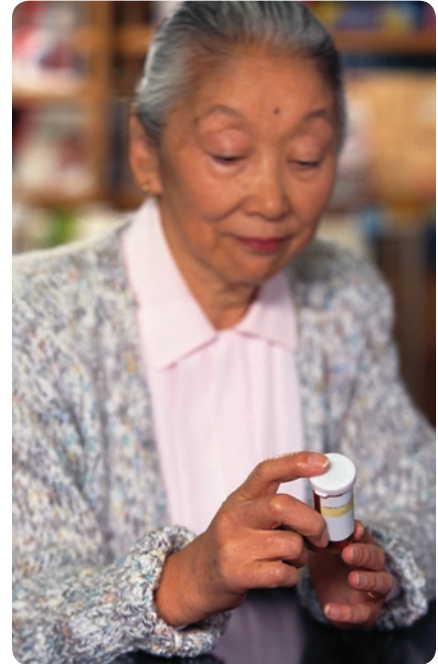


Making Sense of Vytorin Concerns

Q & A with Robert Temple, M.D.

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Q. What is Vytorin?

A. Vytorin is one tablet that combines two cholesterol-lowering drugs—simvastatin (Zocor), a statin made by Merck & Co., and ezetimibe (Zetia), made by Schering-Plough Pharmaceuticals—to help lower bad cholesterol (low-density lipoprotein, or LDL) further. Simvastatin works in the liver to prevent the formation of cholesterol (as do all statin medications), while ezetimibe works by preventing the absorption of cholesterol from the intestine.

Q. What is the ENHANCE study?

A. About four years ago, Merck and Schering-Plough began a study—Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression, or ENHANCE—that compared the effect of ezetimibe combined with simvastatin (Vytorin) to simvastatin alone. The patients in the study were people with a genetic condition of

very high cholesterol called familial hypercholesterolemia. Through images taken with ultrasound, the study evaluated the thickness of the walls of the blood vessels of the neck (carotid arteries). Some studies indicate that increased thickness of the carotid artery walls is associated with an increased risk for cardiovascular disease.

ENHANCE did not try to show an effect of Vytorin on important outcomes, such as the chance of a heart attack or stroke. Rather, it was an imaging study of what is often called a biomarker—in this case, the thickness of the blood vessel walls.

Q. What were the results of the ENHANCE study?

A. While the combination drug Vytorin did better at lowering LDL cholesterol levels than treatment with simvastatin alone, the effect of Vytorin on carotid artery wall thickness was no greater than that observed with simvastatin by itself.

The results were disappointing,

of course, but they do not give the answer about the value of ezetimibe. At this point we know that ezetimibe lowers cholesterol modestly (not nearly as much as a statin), but we do not have definitive evidence that it lowers the risk for cardiovascular disease. The answer to whether it does should come from a large (18,000-patient) outcome study that will examine the effect of ezetimibe added to simvastatin on cardiovascular outcomes. That study is underway but will not be completed for several years.

It is not clear why the lower levels of LDL cholesterol in patients who took Vytorin did not lead to favorable changes in carotid artery wall thickness, compared to patients treated with simvastatin alone. FDA is now reviewing the final results from the ENHANCE study.

Q. Does the Vytorin situation call into question the value of lowering cholesterol levels or the benefits of statins?

A. No. There is overwhelming evidence from many studies that people with elevated LDL cholesterol—a very well-established risk factor for heart disease—reduce their risk of a heart attack or stroke and death by lowering cholesterol with a statin. FDA’s initial approval of cholesterol medications is based on a drug’s ability to demonstrate successful lowering of LDL cholesterol. But every statin to date has been shown in a large outcome study to improve cardiovascular outcome, and labeling for all drugs, except for the most recently approved statin, Crestor, states this clearly. A similar finding has been reported for Crestor, but the study has not yet been reviewed by FDA.

Q. Why, then, the recent public uncertainty about the value of lowering LDL cholesterol, based on the small Vytorin study?

A. We think many people may have misunderstood both the intent and the results of ENHANCE. The study was designed to show an added benefit of ezetimibe on a biomarker and clearly failed to do so. But this does not tell you whether lower cholesterol with ezetimibe will prove useful. The results of the study were released online in the *New England Journal of Medicine (NEJM)* in January 2008, accompanied by news reports asking whether the results have shaken confidence in the value of lowering cholesterol, even using statins.

Although the study could perhaps lead to doubts about ezetimibe—noting again that its lack of effect was on a biomarker—it casts no doubt at all on the value of lowering cholesterol with a statin. Unfortunately, the statins, which have repeatedly been shown to give large reductions in cholesterol levels and a lower risk of dying from heart disease, were also being characterized as having uncertain benefits.

In fact, there is no basis at all for questioning the cardiovascular ben-

efits of statins in reducing the rate of death, heart attack, and stroke in people at risk from elevated LDL cholesterol. And we are worried that some people might suddenly stop taking their statins or other preventive medicines, such as antihypertensives, either because they misunderstood news reports or are affected by a more general sense of doubt.

We already know that people tend to stop taking all long-term drugs, including statins, when they’re on them. And I’m very concerned that aspects of the Vytorin discussion will lead to people becoming indifferent to an extremely important measurement—LDL cholesterol.

Q. What are the benefits of lowering your cholesterol?

A. Cholesterol is essential to the formation of certain hormones. But where LDL cholesterol levels are too high, they cause or accelerate the development of arteriosclerotic plaques (fatty deposits) in blood vessels in the heart or brain, increasing the chance of a heart attack or stroke. According to the Centers for Disease Control and Prevention, heart disease is the leading cause of death for both women and men in the United States. As mentioned, statins have been shown in numerous studies to lower the risk of heart disease and stroke. A simple blood test by your doctor will measure the different kinds of cholesterol in the body, and will allow the doctor to advise on effective treatment.

Q. What is your advice for consumers?

A. People should not misunderstand ENHANCE and think it means that elevated LDL cholesterol need not be lowered. To do so could mean significant personal and public health consequences if it drives them away from continuing to reduce their risk of heart disease through lowering their

cholesterol. People should not stop taking Vytorin or any other drug containing a statin without their doctor’s recommendation, even if they have concerns about the study. Patients can discuss with their doctors whether they should take a larger statin dose or add ezetimibe to control LDL cholesterol adequately. The results with statins make it overwhelmingly clear that controlling LDL cholesterol is essential. [FDA](#)

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Controlling Cholesterol with Statins

www.fda.gov/consumer/updates/statins051608.html

FDA Early Communication About an Ongoing Data Review for Ezetimibe/Simvastatin (marketed as Vytorin), Ezetimibe (marketed as Zetia), and Simvastatin (marketed as Zocor)

www.fda.gov/cder/drug/early_comm/ezetimibe_simvastatin.htm

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