

New Questions on Treating Cholesterol : NYTimes January 17,2008
Study Reveals Doubt on Drug for Cholesterol

For decades, the **theory** that lowering cholesterol is always beneficial has been a core principle of cardiology. It has been **accepted by doctors and used by drug makers to win quick approval for new medicines to reduce cholesterol**. But now some prominent cardiologists say the results of **two recent clinical trials have raised serious questions about that theory**.

“The idea that you’re just going to lower LDL and people are going to get better, that’s too simplistic, much too simplistic,” said Dr. Eric J. Topol, a cardiologist and director of the Scripps Translational Science Institute in La Jolla, Calif.

For patients and drug companies, the stakes are enormous. Led by best sellers like Lipitor from Pfizer, **cholesterol-lowering medicines, taken by tens of millions of patients daily, are the largest drug category worldwide, with annual sales of \$40 billion**.

Despite widespread use of the drugs, though, heart disease remains the biggest killer in the United States and other industrialized nations, and many people still have cholesterol levels far higher than doctors recommend..

Because the link between excessive LDL cholesterol and cardiovascular disease has been so widely accepted, the Food and Drug Administration generally has not required drug companies to prove that cholesterol medicines actually reduce heart attacks before approval. They have not had to conduct so-called outcome or events trials beforehand, which are expensive studies that involve thousands of patients and track whether episodes like heart attacks are reduced.

So far, proof that a drug lowers LDL cholesterol has generally been enough to lead to approval. Only then does the drug’s maker begin an events trial. And until the results of that trial are available, a process that can take several years, doctors and patients must accept the medicine’s benefits largely on faith.

Nonetheless, the multistep process has worked well for several cholesterol drugs — including Lipitor and Zocor, which are in a class of drugs known as statins. In those cases, the postapproval trials confirmed that the drugs reduce heart attacks and strokes, adding to confidence about the link between cholesterol and heart disease. Doctors **generally believe that the amount by which cholesterol is lowered, not the method of lowering it, is what matters**.

That continues to be the assumption of ****Dr. Scott M. Grundy, a professor of medicine at the University of Texas Southwestern Medical Center who was the chairman of a panel in 2001 that set national guidelines for cholesterol treatment****.

“LDL lowering, however it occurs, delays development of coronary atherosclerosis and reduces risk for heart attack,” Dr. Grundy said this week. In atherosclerosis, plaque builds up in the arteries, eventually leading to blood clots and other problems that cause heart attacks and strokes.

In the last 13 months, however, the failures of two important clinical trials have thrown that hypothesis into question.

First, Pfizer stopped development of its experimental cholesterol drug torcetrapib in December 2006, when **a trial involving 15,000 patients showed that the medicine caused heart attacks and strokes.** That trial — somewhat unusual in that it was conducted before Pfizer sought F.D.A. approval — **also showed that torcetrapib lowered LDL cholesterol while raising HDL, or good cholesterol.**

Torcetrapib’s failure, Dr. Taylor said, shows that **lowering cholesterol alone does not prove a drug will benefit patients.**

Then, on Monday, Merck and Schering-Plough announced that Vytorin, which combines Zetia with Zocor, had failed to reduce the growth of fatty arterial plaque in a trial of 720 patients. In fact, patients taking Vytorin actually had more plaque growth than those who took Zocor alone.

Despite those drawbacks, that trial, called Enhance, also showed that patients on Vytorin had lower LDL levels than those on Zocor alone. **For the second time in just over a year, a clinical trial found that LDL reduction did not translate into measurable medical benefits.**

The Enhance trial was not an events trial and was not intended to study whether Zetia or Vytorin were effective at reducing heart attacks.

****Note: Five of the 14 panel members (including Dr. Grundy) who set the 2001 Cholesterol Guidelines were consultants to -- or received honorariums from -- Pfizer, Merck, Bristol-Myers or other companies.**

This article is nothing less than stunning.

There is no science supporting the cholesterol theory and its widespread use. In fact, scientific studies only show that “the medicine increases the rate of heart attack and stroke!”

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