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Cholesterol As a Danger Has Skeptics

By ALEX BERENSON

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 — and the value of two widely used cholesterol-lowering medicines, Zetia and its sister drug, Vytorin. Other new cholesterol-fighting drugs, including one that Merck hopes to begin selling this year, may also require closer scrutiny, they say.

"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. LDL, or low-density lipoprotein, is the so-called bad cholesterol, in contrast to high-density lipoprotein, or HDL.

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

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United States and other industrialized nations, and many people still have cholesterol levels far higher than doctors recommend.

As a result, drug companies are investing billions of dollars in experimental new cholesterol-lowering medicines that may eventually be used alongside the existing drugs. If the new questions result in slower approvals, it would be yet another handicap for the drug industry.

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.

"You've got a huge chasm between F.D.A. licensure and a clinical events trial," said Dr. Allen J. Taylor, the chief of cardiology at Walter Reed Army Medical Center.

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.

Should lowering a patient's cholesterol be all that matters?

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. But the growth of fatty plaque is closely correlated with heart attacks and strokes.

Without data from events trials for Zetia and Vytorin, no one can be certain if the drugs help or hurt patients. But Merck and Schering did not begin an events trial for the drugs until 2006, nearly four years after the F.D.A. approved Zetia. That trial will not be completed until 2011.

Dr. Robert M. Califf, the vice chancellor for clinical research at Duke University, and a co-lead investigator on the Zetia trial still under way, said companies should have started the trials more quickly. "Outcome trials ought to start when you know you're going to get on the market," he said.

On Tuesday, the American Heart Association called for the Zetia outcome trial to be completed as quickly as possible.

Merck has asked the F.D.A. to approve its drug Cordaptive, which raises HDL cholesterol and lowers LDL, without waiting for the results of an events trial. Merck has begun an events trial for Cordaptive, but data will not be available until 2013.

Merck has submitted the application for Cordaptive and has said it expects an answer from the F.D.A. before July. Doctors, patients and the drug industry will be waiting to see whether regulators are still willing to accept the theory that lower cholesterol is always a good thing.