

Doctors Wary After Cholesterol Drug Flop

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CHICAGO (AP) - Leading doctors urged a return to older, tried-and-true treatments for high cholesterol after hearing full results Sunday of a failed trial of Vytorin.

Millions of Americans already take the drug or one of its components, Zetia. But doctors were stunned to learn that Vytorin failed to improve heart disease even though it worked as intended to reduce three key risk factors.

"People need to turn back to statins," said Yale University cardiologist Dr. Harlan Krumholz, referring to Lipitor, Crestor and other widely used brands. "We know that statins are good drugs. We know that they reduce risks."

The study was closely watched because Zetia and Vytorin have racked up \$5 billion in sales despite limited proof of benefit. Two Congressional panels launched probes into why it took drugmakers nearly two years after the study's completion to release results.

Results were presented at an American College of Cardiology conference in Chicago Sunday and published on the Internet by the New England Journal of Medicine.

Doctors have long focused on lowering LDL or bad cholesterol as a way to prevent heart disease. Statins like Merck & Co.'s Zocor, which recently came out in generic form, do this, as do niacin, fibrates and other medicines.

Vytorin, which came out in 2004, combines Zocor with Schering-Plough Corp.'s Zetia, which went on sale in 2002 and attacks cholesterol in a different way.

The study tested whether Vytorin was better than Zocor alone at limiting plaque buildup in the arteries of 720 people with super high cholesterol because of a gene disorder.

The results show the drug had "no result - zilch. In no subgroup, in no segment, was there any added benefit" for reducing plaque, said Dr. John Kastelein, the Dutch scientist who led the study.

That happened even though Vytorin dramatically lowered LDL, fats in the blood called triglycerides and a measure of artery inflammation - CRP.

Some doctors noted that hormone pills for menopausal women and torcetrapib, a promising cholesterol drug Pfizer Inc. recently abandoned, also lowered cholesterol but were found in big studies to raise heart risks, not lower them.

Another ominous sign was the decision Friday by other researchers to expand enrollment in a more pivotal study of Vytorin to 18,000 people because early results suggest it will be harder than anticipated to see if it is any better than Zocor alone.

"It will be 2012 - ten years after the drug was introduced - before we know the answer," said Dr. Steven Nissen, a Cleveland Clinic cardiologist who has no role in the studies and has criticized the drugmakers over the one reported Sunday.

Dr. Robert Spiegel, chief medical officer for Schering-Plough, said the study was done "with the highest integrity" and that doctors can believe the results "because of the time we took to make sure the data are right."

"We were disappointed that it was not a very balanced panel discussion" by the heart doctors who urged their peers to focus on more established treatments.

However, Kastelein said the data were far more consistent than anticipated and ample to show that the drug simply did not work.

"A lot of us thought that there would be some glimmer of benefit," said Dr. Roger Blumenthal, a Johns Hopkins University cardiologist and spokesman for the American Heart Association.

Many doctors have prescribed Vytorin without trying older, proven medications first, as guidelines advise. The key message from the study is "don't do that," Blumenthal said.

No one should ever stop any heart drug without talking with their doctors, heart specialists stressed.

However, doctors "should be thinking twice," said Duke University cardiologist Dr. Robert Califf. He takes the drug himself because he cannot tolerate the high dose of statins he otherwise would need.

Dr. James Stein, director of preventive cardiology at the University of Wisconsin-Madison, said many doctors prescribe Zetia and Vytorin because they seem to be safe ways to get cholesterol down quickly, without annoying side effects like flushing that some other medicines carry.

Stein, who has consulted for Schering-Plough, said that after six years on the market, it would have been good to see better results on a drug so many doctors believed would help, "but the reason we do research is so we don't have to rely on our 'beliefs' - we can rely on data."

The New England Journal also published a report showing that Vytorin and Zetia's use soared in the United States amid a \$200 million advertising blitz. In Canada, where marketing drugs directly to consumers is not allowed, sales were four times lower.

Merck is based in Whitehouse Station, N.J.; Schering-Plough, in Kenilworth, N.J.

In addition to the two Congressional committee probes, New York State Attorney General Andrew Cuomo subpoenaed the companies in a similar probe in January.

"While these corporations profited, Americans were left in the dark," Cuomo said in a written statement Sunday. "The millions who take this drug, taxpayers who subsidize its use through the Medicaid and Medicare programs, and Merck and Schering-Plough's investors deserve to know why it took so long for the results to be made public. This new information underscores our concerns and advances our investigation, which we will pursue aggressively."

On the Net:

New England Journal: www.nejm.org

Cardiology conference: www.acc.org

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