NATURE | NEWS

Drug trial supports importance of low cholesterol to treat heart disease

Results bolster the practice of using medicines to drive down cholesterol levels.

Heidi Ledford

17 November 2014

Jonathan Drake/Bloomberg via Getty

The ability of cholesterol-lowering medications to prevent heart attacks and stroke has come under scrutiny.

A popular but controversial cholesterol drug reduces the risk of cardiovascular events such as heart attacks and stroke, researchers say. The drug, called ezetimibe, had been shower to lower cholesterol levels, but its ability to combat heart disease was in dispute.

But now ezetimibe, made by Merck of Whitehouse Station, New Jersey, has been found to lower the number of cardiovascular events by 6.4% when given with another cholesterol drug. The effect is significant but small; still, some scientists say that the results affirm the 'lower is better' hypothesis: that reducing levels of low-density lipoprotein (LDL) cholesterol (often called 'bad' cholesterol) lowers the risk of cardiovascular events.

"The question that everyone had was, 'Would this added lowering of LDL cholesterol translate into a real clinical benefit?'" says cardiologist Christopher Cannon of the Brigham and Women's Hospital in Boston, Massachusetts. "The answer was yes."

That finding, which Cannon presented on 17 November at the American Heart Association meeting in Chicago, Illinois, may come as a relief not only to Merck, but to other pharmaceutical companies — particularly those developing cholesterol drugs (see 'A gene of rare effect').

It is much faster and cheaper to win drug approval on the basis of lowering cholesterol than of reducing cardiovascular events. Cholesterol levels change rapidly in response to medication, and they are easy to measure. Cardiovascular events, in contrast, are relatively rare. Trials to study them must enrol thousands of people to achieve statistically significant numbers of events.

The trial that Cannon presented today, code-named IMPROVE-IT, enrolled more than 18,000 patients and took 9 years to complete.

But Harlan Krumholz, a cardiologist at Yale University in New Haven, Connecticut, warns against the assumption that lower is always

better when it comes to LDL cholesterol. “I don’t think you can extrapolate from this to say that any drug that lowers cholesterol is better,” he says. “We have lots of examples where that doesn’t happen.”

Uncertain significance

Ezetimibe reduces cholesterol absorption by inhibiting the activity of a protein called NPC1L1, which transports free cholesterol into cells. When combined with a statin, another cholesterol-lowering drug, ezetimibe lowers cholesterol by an extra 20% compared to the statin alone.

This seemed to bode well for the drug’s impact on heart health when the US Food and Drug Administration approved ezetimibe in 2002. But in 2008, researchers found that the drug had no impact on the thickness of artery walls in the neck and thigh — a measure of fatty plaque build-up[1]. This plaque build-up is thought to contribute to heart disease by restricting blood flow.

The results cast doubt on the usefulness of ezetimibe and of the importance lowering cholesterol in general. Statins had been shown to reduce the risk of heart disease, but that was not true for other medications that lower LDL cholesterol — including niacin and drugs called fibrates.

Hopes for ezetimibe were bolstered last week when a genetic analysis of 7,364 people with heart disease and 14,728 controls found that people who had a rare mutation that inactivates the NPC1L1 protein had lower LDL cholesterol levels and a lower risk of coronary heart disease[2].

Cannon tackled the controversy by presenting data from his clinical trial, which compared about 9,000 patients receiving a statin called simvastatin to another 9,000 receiving the statin and ezetimibe. (Neither the patients nor the researchres knew which patients had been assigned which drugs.) The rate of cardiovascular events was 34.7% in patients receiving only the statin, and 32.7% in patients receiving both drugs.

“The study affirms the central role of intensive LDL reduction in the prevention of recurrent cardiovascular events,” says Neil Stone, a cardiologist at Northwestern University in Chicago, who was not involved with the study.

But Stone warns that the trial was carried out in high-risk patients, a common practice used to boost the likelihood of cardiovascular events. “The data don’t speak to the use of ezetimibe in patients with low risk,” he adds.

For Krumholz, the concern is that people will become overly confident in other drugs that lower cholesterol, in the absence of data on cardiovascular events. “The problem is that drugs can have multiple effects,” he says. “You can’t know for sure what the net effect is on people without formally testing it.”

Nature | doi:10.1038/nature.2014.16360

References

1. Kastelein, J. J. P. *et al. N. Engl. J. Med.* **358**, 1431–1443 (2008).
2. The Myocardial Infarction Genetics Consortium Investigators. *N. Engl. J. Med.* http://dx.doi.org/10.1056/NEJMoa1405386 (2014).