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Evacetrapib impacts cholesterol but doesn't reduce cardiovascular events

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Cleveland Clinic researchers studying evacetrapib have shown that despite reducing levels of low-density lipoprotein (LDL, or "bad" cholesterol) by 37 percent and raising levels of high-density lipoprotein (HDL, or "good" cholesterol) by 130 percent, the drug failed to reduce rates of major cardiovascular events, including heart attack, stroke, angina or cardiovascular death.

The phase 3, multi-center clinical trial was discontinued in October 2015, on the recommendation of the independent Data Monitoring Committee after preliminary data suggested the study would not meet its primary endpoint of a reduction in major cardiovascular events. The research is being presented at the American College of Cardiology's 65th

Annual Scientific Session

"Here we have a paradox. The drug more than doubled HDL and lowered LDL levels by as much as many statins, but had no effect on cardiac events," said Steve Nissen, M.D., chairman of Cardiovascular Medicine at Cleveland Clinic. "These findings illustrate the importance of performing large, high-quality outcome trials. Just looking at the effects a therapy has on cholesterol levels doesn't always translate into clinical benefits."

The ACCELERATE trial involved more than 12,000 patients at more than 540 sites who were at high risk for serious cardiovascular problems. They were randomized to receive either 130 milligrams of evacetrapib or a placebo daily, along with standard medical therapy throughout the trial. Study participants either had an acute coronary syndrome 30 days to one year before enrolling, had cerebrovascular atherosclerotic disease, had peripheral vascular disease, or had both diabetes and coronary artery disease.

Those receiving evacetrapib saw their LDL cholesterol levels reduced by 37 percent and their HDL levels increased by 130 percent. Still, the improvements in cholesterol did not result in any reduction in the occurrence of cardiovascular death, heart attack, stroke, coronary artery bypass surgery or hospitalization for chest pain due to unstable angina. Researchers observed a borderline significant reduction in all-cause mortality in the evacetrapib group; however, that was not driven by a decrease in cardiovascular death.

"We were certainly hoping for different results, and are trying to understand why we didn't see a benefit from this drug" said Dr. A. Michael Lincoff, M.D., director of the Cleveland Clinic Coordinating Center for Clinical Research (C5Research) and a Principal Investigator on the study. "The trial raises questions about the benefits of raising

HDL and the future of this class of drugs."

Despite widespread use of statins, many patients continue to experience cardiovascular events. Therefore, considerable efforts have been put into investigating whether the protective benefits of HDL cholesterol could be targeted as a form of therapy.

Evacetrapib is in a class of drugs known as cholesteryl ester transfer protein (CETP) inhibitors. They work by disrupting the process which normally transfers cholesterol from HDL cholesterol to LDL cholesterol in the body. Animal and genetic studies have suggested that CETP deficiency is cardioprotective; however, this is the third failure in this class of drugs. Results of a phase 3 clinical trial of the first drug, torcetrapib, showed an increase in adverse outcomes. Trials were stopped for dalcetrapib, a second CETP inhibitor, when it was also found to be ineffective. Evacetrapib was thought to be a promising approach because it is a potent CETP inhibitor and lacks the toxicity of torcetrapib.

Safety concerns were not raised by the trial, and the study didn't reveal any major side effects.

Provided by Cleveland Clinic