Evacetrapib fails to reduce major adverse cardiovascular events

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Despite lowering low-density lipoprotein (LDL), known as "bad" cholesterol, while markedly increasing levels of high-density lipoprotein (HDL), or "good" cholesterol, a large clinical trial to investigate the cholesterol drug evacetrapib was discontinued early after a preliminary analysis showed it did not reduce rates of major adverse cardiovascular events, according to research presented at the American College of Cardiology's 65th Annual Scientific Session.

The favorable effects on cholesterol did not translate into any reduction in the study's primary endpoint: the amount of time until cardiovascular death, heart attack, stroke, coronary artery bypass surgery or hospitalization for chest pain due to unstable angina, a restriction in the flow of blood through the heart's arteries.

"Here we've got an agent that more than doubles the levels of good cholesterol and lowers bad cholesterol and yet has no effect on clinical events," said Stephen Nicholls, M.B.B.S, Ph.D., a professor at Australia's University of Adelaide, cardiologist at Royal Adelaide Hospital and the study's lead author. "We were disappointed and surprised by the results."

The study was a phase 3, randomized, double-blind trial conducted in approximately 540 global health centers involving more than 12,000 patients at high risk for serious cardiovascular problems. Participants were randomized to receive either 130 milligrams of evacetrapib or a placebo daily for at least 18 months. All patients also received standard medical therapy throughout the trial, which in a vast majority of cases

included treatment with statins or other cholesterol-lowering drugs.

On average, patients taking evacetrapib lowered their LDL cholesterol by 37 percent and increased their HDL cholesterol by 130 percent compared with patients taking a placebo. However, there was no difference between the two groups in terms of the study's primary endpoint.

The findings make evacetrapib the third failure in a class of drugs known as cholesteryl ester transfer protein (CETP) inhibitors, which are designed to disrupt the natural process by which HDL cholesterol is converted into LDL cholesterol in the body. The first such drug, torcetrapib, was abandoned after a phase 3 clinical trial revealed it increased the risk of cardiovascular events and death. Development of a second CETP inhibitor, dalcetrapib, was stopped when a phase 2 clinical trial found the drug to be ineffective.

"There has been, and continues to be, a lot of confusion about what's going on with this class of drugs, since we don't yet have one that can be brought to the clinic to prevent heart attack and stroke in our patients," Nicholls said. "As we close out the trial, we're trying to understand how a drug that seems to do all the right things in terms of blood cholesterol levels doesn't then translate into reducing clinical events."The results raised no safety concerns for evacetrapib and did not reveal any major side effects. Nicholls said the findings could offer evidence challenging conventional thinking regarding the benefits of HDL cholesterol in protecting against cardiovascular problems. Another possible explanation is that existing treatments, such as statins, are already so effective at improving cardiovascular outcomes that it has become more difficult to further improve outcomes in high-risk patients. Alternatively, the results could indicate that evacetrapib's active ingredient or the biological pathway it is designed to affect simply has no effect on cardiovascular risk.

All study participants either had an acute coronary syndrome such as a heart attack or unstable angina 30 days to one year before enrolling; had cerebrovascular atherosclerotic disease, in which the arteries that supply blood to the brain become constricted; had peripheral vascular disease, a group of disorders affecting blood vessels outside of the heart and brain; or had both diabetes and coronary artery disease.

"We tested the drug in high-risk patients because they are the patients with the greatest need for new drugs above and beyond what we already use in our clinics," Nicholls said. "Low risk patients could be another group of patients that could potentially benefit from this drug, but we didn't test that and to do so would require an extraordinarily large study that asks a different question from the one our study was designed to address."

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