Study: Cholesterol substantially reduced with oral PCSK9 inhibitor

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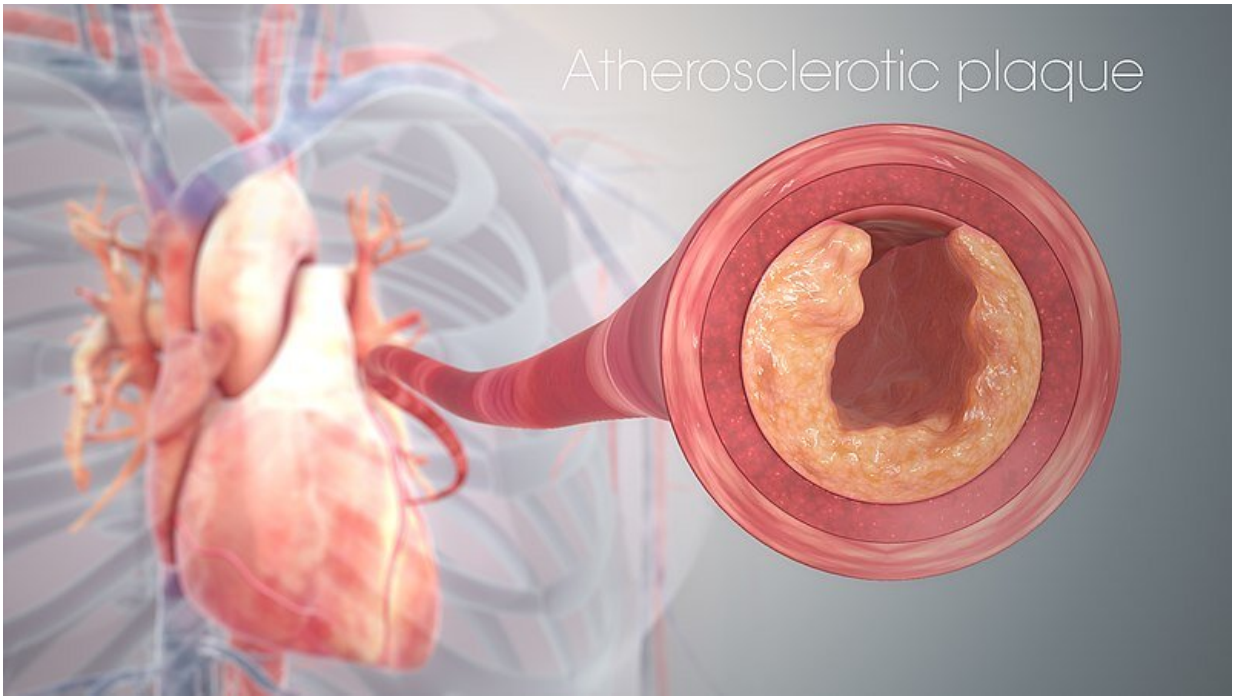

Atherosclerosis of the heart's arteries reduces surface area and oxygen carrying capacity. Credit: http://www.scientificanimations.com/Wikimedia Commons, CC BY-SA

A new study led by Baylor College of Medicine and presented at the American College of Cardiology's Annual Scientific Session together with World Congress of Cardiology found that an oral PCSK9 inhibitor called MK-0616 reduced LDL, or "bad," cholesterol by more than 60%.

The study was simultaneously published online in the *Journal of the American College of Cardiology* at the time of presentation.

MK-0616, an experimental oral proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, substantially reduced levels of low-density lipoprotein (LDL) cholesterol in people with high cholesterol and/or heart disease related to clogged arteries.

MK-0616 is one of the first oral PCSK9 inhibitors to be tested in clinical trials. All the currently available PCSK9 inhibitors must be administered through an injection under the skin. Like other PCSK9 inhibitors, MK-0616 is designed to reduce levels of LDL cholesterol in people who have too much of it, thereby lowering their risk of heart disease. PCSK9 inhibitors are usually taken alongside statins, the standard first-line therapy for treating high cholesterol, and can be used alone in people who cannot take statins.

Results from this phase II trial showed MK-0616 reduced LDL cholesterol by about 60% among people taking 30 mg or 18 mg daily, compared to those taking a placebo.

"This is a highly effective compound that was well tolerated," said Dr. Christie M. Ballantyne, professor and director of the Center for Metabolic Disease Prevention at Baylor and the study's first author. "MK-016 could offer another potential option. Between this and statins and the other therapies we have, we should be able to basically treat almost everybody in terms of LDL cholesterol."

For the study, researchers enrolled 381 adults who had either a history of heart disease or risk factors for heart disease with elevated levels of LDL cholesterol. About 60% of the participants were taking statins at the start of the study, with about one-quarter receiving high-intensity statin therapy.

Participants were randomly assigned to one of five groups; one group received a placebo while the other groups received MK-0616 at one of four doses (6, 12, 18, or 30 mg) per day. Participants continued taking the placebo or study drug for eight weeks and then discontinued their assigned regimen. Researchers assessed the change in LDL cholesterol between baseline and week eight (the study's primary endpoint) and tracked adverse events through week 16.

At eight weeks, MK-0616 doses demonstrated significant reductions in LDL cholesterol, which dropped by more than 60% in those receiving 30 mg, by 59% in those receiving 18 mg, by over 55% in those receiving 12 mg and by 41% in those receiving 6 mg daily, relative to those receiving placebo.

They also experienced large reductions in non-high-density lipoprotein (non-HDL) cholesterol and apolipoprotein B (ApoB). These tests measure total "bad" cholesterol and particles that carry cholesterol in the blood, which can indicate a buildup of plaques in the arteries.

MK-0616 is designed to work via the same biological mechanism that available injectable PCSK9 inhibitors do, by helping the body clear LDL cholesterol more effectively. If further studies confirm the oral drug has a similar level of efficacy and safety as the injectable forms, researchers say having a PCSK9 inhibitor in a pill form could help to lower costs, increase convenience and expand access to this cholesterol-lowering agent to more patients.

"I was told early on that developing an oral PCSK9 inhibitor is impossible," said Ballantyne. "But the technology keeps advancing. It's very exciting to see the tremendous advances in understanding the pathways and finding ways to make a challenging target like PCSK9 treatable with a once-daily pill."

Researchers said the study found no evidence of serious side effects and no evidence that side effects increased with higher doses of MK-0616. However, longer studies involving more participants are needed to assess potential side effects more definitively.

As a phase II study, the trial was limited by a relatively short duration and small sample size. Researchers will continue to study how the drug behaves within the body to determine the efficacy and safety of this therapy in a phase III clinical trial program being planned.

More information: Christie M. Ballantyne et al, Efficacy and safety of the oral PCSK9 inhibitor MK-0616: a phase 2b randomized controlled trial, *Journal of the American College of Cardiology* (2023). DOI: 10.1016/j.jacc.2023.02.018

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