Novel PCSK9 inhibitor cut LDL cholesterol levels by more than half

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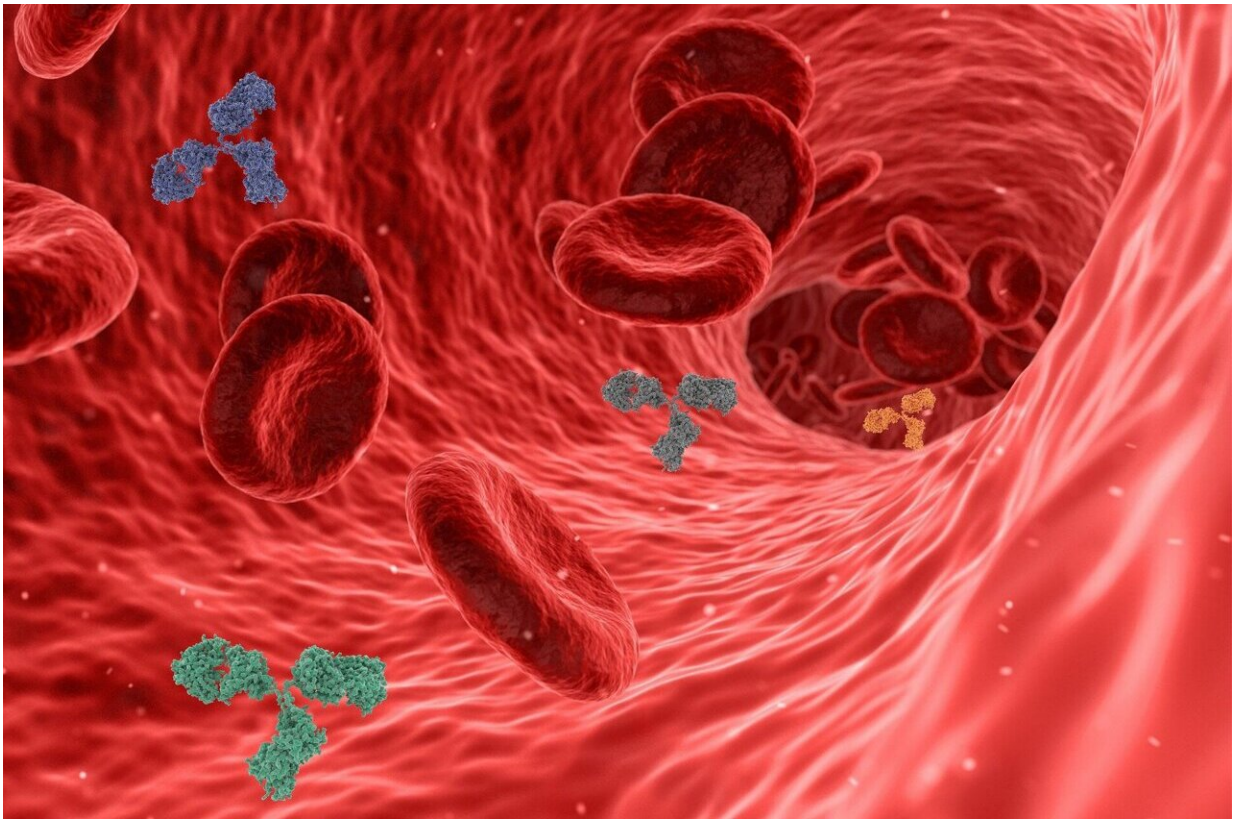

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Among patients at high or very high risk for a heart attack or stroke, the addition of the investigational drug lerodalcibep to standard cholesterol-lowering medication for one year reduced LDL, or "bad" cholesterol,

levels by more than half on average, compared with placebo.

In addition, 90% of patients treated with lerodalcibep, versus 16% of those on placebo, attained the newer, more stringent guideline-recommended LDL targets set by the American College of Cardiology (ACC) and other expert organizations. The research was presented at the ACC's Annual Scientific Session.

"These are the first long-term data for lerodalcibep, which show it to be both highly effective and safe after one year of follow-up," said Eric Klug, MBBCh, MMed, of the University of Witwatersrand in Johannesburg, South Africa, and the study's lead author.

"We have demonstrated persistent LDL-cholesterol-lowering efficacy over 52 weeks, with over 90% of patients achieving both a reduction greater than 50% and the new much lower LDL targets. In addition, lerodalcibep was well-tolerated, with minimal adverse effects."

Lerodalcibep is a novel inhibitor of PCSK9, a protein in the liver that reduces the liver's ability to clear LDL cholesterol from the circulation. PCSK9 inhibitors block the PCSK9 protein, enabling the liver to dispose of more LDL cholesterol, which in turn lowers blood levels of LDL cholesterol, Klug said. Lerodalcibep is given as a low-dose (1.2 mL) monthly injection.

Unlike existing approved PCSK9 inhibitors, Klug said lerodalcibep does not need refrigeration, is a smaller injectable (based on volume or amount), and patients can administer their own injections. Previous studies have shown that the drug significantly reduced LDL cholesterol levels for up to 24 weeks with no safety concerns.

Recommendations as to how low "bad" cholesterol levels should go in patients who are at high or very high risk for a heart attack or stroke

have recently changed. Since 2022, the ACC, American Heart Association, and European Society of Cardiology (ESC) all recommend LDL cholesterol goals of no more than 55 mg/dL for patients with cardiovascular disease or who are at very high risk for a heart attack or stroke and no more than 70 mg/dL for high-risk patients.

All organizations recommend additional treatment for patients who are unable to meet these goals with statins alone.

"Statins are, and should continue to be, the foundation for reducing LDL cholesterol levels, as they are well proven over the last 30 years to reduce risk for heart disease and strokes," Klug said. "For many patients, however, even taking the maximum dose of a statin that they can tolerate, as well as additional non-statin oral agents, does not reduce their LDL cholesterol to a low-risk level."

Studies conducted in both the U.S. and Europe have shown that as many as 80% of high-risk, statin-treated patients are not currently meeting the new LDL cholesterol goals, including those who are also taking a second, non-statin cholesterol-lowering drug, Klug said.

"It's for these patients that additional treatment with PCSK9 inhibitors is recommended," he said.

The LIBerate-HR trial enrolled 922 patients, whose average age was 64.5, in 11 countries; 45% of the patients were women, 77.9% were White, and 22.1% were Black, multiracial, or South Asian. Just over half (52%) had not yet had a heart attack or stroke but were at high or very high risk for one.

The average LDL cholesterol level at study entry was about 116 mg/dL, although 84% of the patients were taking a statin, some at high-intensity doses, and 17% were also taking a second cholesterol-lowering drug,

ezetimibe. About a quarter of patients also had diabetes, and 10% had familial (inherited) hypercholesterolemia (FH).

Patients were randomly assigned to one of two groups: Two-thirds received monthly treatment with 300 mg (1.2 mL) of lerodalcibep, and one-third a monthly dose of matching placebo. Both groups continued their diet and existing cholesterol-lowering medications. The study was triple-blinded, meaning that neither the patients, study staff doctors, nor the trial sponsors knew who was receiving lerodalcibep or placebo until the study was over.

The primary endpoints were the percentage change in patients' LDL cholesterol levels with lerodalcibep compared to placebo from study entry to one year and the average of LDL cholesterol levels at weeks 50 and 52. Secondary endpoints included safety, changes in levels of other lipids that influence cardiovascular risk, and achievement of the ESC and ACC/AHA-recommended LDL cholesterol levels.

At one year, 824 patients (89%) had completed the study, with a similar dropout rate in both the lerodalcibep and placebo groups. Patients assigned to lerodalcibep achieved an average placebo-adjusted percentage reduction in LDL cholesterol of between 56% (at week 52) and 63% (the average of weeks 50 and 52).

More than 90% of patients in the lerodalcibep group achieved a reduction of 50% or more in their LDL cholesterol levels and attained the target LDL cholesterol level for their risk group during the 52-week study. In the placebo group, 16% of patients achieved both goals.

Among patients treated with lerodalcibep, levels of apolipoprotein B—a protein that transports LDL cholesterol through the bloodstream—fell by an average of 43%, and levels of lipoprotein (a), another "bad" cholesterol variant that contributes to cardiovascular risk, fell by 33%.

"Age, gender, race, body mass index, baseline LDL cholesterol level, intensity of statin use, presence of diabetes or FH—none of these factors altered the outcome favoring lerodalcibep," Klug said.

A mild or moderate reaction, such as redness, itching, or bruising, at the site of the injection, was the most common adverse event, affecting 6.9% of patients in the lerodalcibep group and 0.3% in the placebo group. However, the number of patients who withdrew from the trial due to these reactions was minimal and similar in the lerodalcibep and placebo groups, he said.

A larger trial with more patients and longer follow-up compared to a placebo is needed to determine whether the amount of LDL lowering seen with lerodalcibep also translates to greater reductions in cardiovascular events and will begin later this year. All the patients who participated in the LIBerate-HR trial are now receiving lerodalcibep and are being studied in an open-label ongoing assessment of the drug for another year.

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