Investigational drug vupanorsen achieves modest reduction in non-HDL cholesterol

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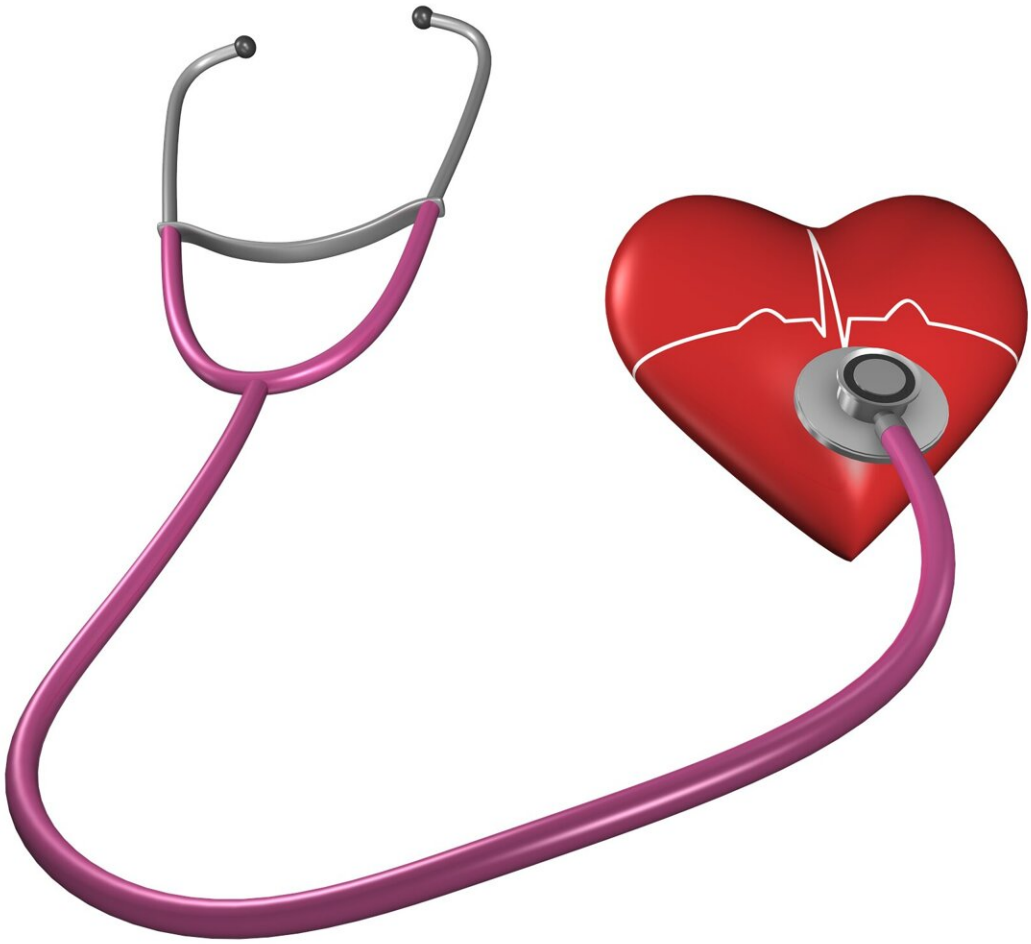

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The investigational drug vupanorsen reduced total levels of non-high-density lipoprotein (non-HDL) cholesterol by up to 28% in patients with high cholesterol who were already taking a cholesterol-lowering statin medication, in a study presented at the American College of Cardiology's 71st Annual Scientific Session. In addition, vupanorsen lowered levels of triglycerides by up to 57% and levels of angiopoietin-like 3 (ANGPTL3), the protein the drug was designed to target, by up to 95%. The drug had more modest effects on low-density lipoprotein (LDL) cholesterol and apolipoprotein B (ApoB) levels.

High levels of non-HDL cholesterol in the blood are associated with a high risk of cardiovascular disease. This risk can be mitigated with cholesterol-lowering drugs such as statins. However, researchers said there is an unmet need for additional cholesterol-lowering strategies for patients who still have high cholesterol after taking statins.

"Vupanorsen reduced non-HDL cholesterol at all doses studied in a statistically significant way and cut triglyceride levels in half. Whether these reductions would be sufficient to translate into a clinically meaningful cardiovascular risk reduction remains unclear," said Brian Bergmark, MD, cardiologist at Brigham and Women's Hospital, investigator for the Thrombolysis in Myocardial Infarction (TIMI) Study Group and the study's lead author.

Vupanorsen is an experimental drug designed to lower non-HDL cholesterol by reducing the production of ANGPTL3, a protein that inhibits enzymes involved in the metabolism of triglyceride and cholesterol. For the trial, researchers enrolled 286 patients at 55 medical centers in the U.S., Canada and Poland. Before the study, participants

had non-HDL cholesterol of 100 mg/dL or higher, triglycerides of 150–500 mg/dL and were already taking a statin.

Participants were randomly assigned to receive either a placebo or one of seven vupanorsen doses ranging from 80 milligrams once per month to 160 milligrams every two weeks via subcutaneous injection. At 24 weeks, those taking vupanorsen had a significant reduction in non-HDL cholesterol, on average, achieving the study's primary endpoint. Additionally, those patients taking vupanorsen had a 41.3%–56.8% reduction in triglycerides, a reduction in low-density lipoprotein (LDL) cholesterol of up to 16.2% and a reduction in apolipoprotein B (ApoB) levels of up to 15.1%. ANGPTL3 levels were reduced by 69.9%–95.2% in those taking vupanorsen.

Participants taking vupanorsen at higher doses saw an increased rate of injection site reactions and elevations in liver enzymes. In addition, the researchers found that vupanorsen use was associated with dose-related increases in liver fat accumulation. This was unexpected, as findings from laboratory studies in animal models suggested the drug could potentially help to lower fat content in the liver.

"Regardless of the future of this compound, we did find out some information that may be quite relevant for future studies," Bergmark said. "There are numerous other compounds targeting this pathway or adjacent metabolic pathways through similar mechanisms, and it will be interesting to see how this plays out for other agents."

Bergmark said it is unclear whether the drug could hold greater benefits for people with particular lipid disorders that lead to extremely high levels of non-HDL cholesterol. He added that a larger sample size could potentially shed more light on how the drug works to reduce cholesterol.

This study was simultaneously published online in *Circulation* at the time

of presentation.

More information: Brian A. Bergmark et al, Effect of Vupanorsen on Non-High-Density Lipoprotein Cholesterol Levels in Statin-Treated Patients With Elevated Cholesterol: TRANSLATE-TIMI 70, *Circulation* (2022). DOI: 10.1161/CIRCULATIONAHA.122.059266