

New medication increases HDL cholesterol and decreases LDL cholesterol levels

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Among patients with sub-optimal low-density lipoprotein cholesterol (LDL-C) or high-density lipoprotein cholesterol (HDL-C) levels, use of the drug evacetrapib alone or in combination with statin medications was associated with significant increases in HDL-C levels and decreases in LDL-C levels, according to a study appearing in the November 16 issue of *JAMA*, a theme issue on cardiovascular disease. The study is being released early online to coincide with its presentation at the American Heart Association Scientific Sessions.

Cardiovascular disease remains the leading cause of death. "Accordingly, considerable efforts have focused on development of novel therapeutic agents designed to address residual [cardiovascular risk](#). Because individuals from the general population with elevations of HDL-C have a reduced incidence of [coronary heart disease](#), it has been assumed that finding an appropriate therapy to increase HDL-C levels would yield substantial [clinical benefit](#). However, development of drugs that increase HDL-C levels has been challenging and fraught with failures, including the premature termination of a large outcomes trial studying the effects of the cholesteryl ester transfer protein (CETP) inhibitor torcetrapib. Despite failure of the first drug in the class, considerable interest remains in CETP inhibition as a [therapeutic strategy](#), by virtue of the ability of these agents to substantially increase HDL-C levels and, in some cases, reduce LDL-C levels," according to background information in the article. "Few studies have documented the efficacy and safety of CETP inhibitors in combination with commonly used statins."

Stephen J. Nicholls, M.B.B.S., Ph.D., of the Cleveland Clinic, and colleagues evaluated the biochemical efficacy, safety, and tolerability of the CETP inhibitor evacetrapib as monotherapy and in combination with statin agents commonly used in clinical practice in patients with dyslipidemia. The [randomized controlled trial](#), which included 398 patients with elevated LDL-C or low HDL-C levels, was conducted from April 2010 to January 2011 at community and academic centers in the United States and Europe. Patients were randomly assigned to receive placebo (n=38); evacetrapib monotherapy, 30 mg/d (n=40), 100 mg/d (n=39), or 500 mg/d (n=42); or statin therapy (n=239) (simvastatin, 40 mg/d; atorvastatin, 20 mg/d; or rosuvastatin, 10 mg/d) with or without evacetrapib, 100 mg/d, for 12 weeks. The primary outcomes measured were percentage changes in HDL-C and LDL-C levels at the beginning of the trial to after 12 weeks of treatment. The average age of the participants was 58 years, and 56 percent were women.

The average lipid levels at the beginning of the study were 55.1 mg/dL for HDL-C and 144.3 mg/dL for LDL-C. The researchers found that as monotherapy, evacetrapib produced dose-dependent increases in HDL-C of 30.0 to 66.0 mg/dL (53.6 percent to 128.8 percent) compared with a decrease with placebo of -0.7 mg/dL (-3.0 percent) and decreases in LDL-C of -20.5 to -51.4 mg/dL (-13.6 percent to -35.9 percent) compared with an increase with placebo of 7.2 mg/dL (3.9 percent). The HDL-C changes were significantly greater among patients with lower levels of HDL-C or higher triglyceride levels at baseline.

When administered in combination with statin therapy, evacetrapib, 100 mg/d, increased HDL-C levels by 42.1 to 50.5 mg/dL (78.5 percent to 88.5 percent) and resulted in greater reductions in LDL-C (-67.1 to -75.8 mg/dL [-11.2 percent to -13.9 percent]) and non-HDL-C compared with effects observed with statin monotherapy. Compared with evacetrapib monotherapy, the combination of a statin and evacetrapib resulted in greater reductions in LDL-C but no greater increase in HDL-C,

consistent with known lipid effects of statins.

There was no difference between evacetrapib and control groups in either the [monotherapy](#) or statin combination studies with regard to the rate of treatment-related adverse events and discontinuation rates.

"These preliminary findings suggest that evacetrapib could be administered with statins and may yield potentially clinically important incremental effects on lipoproteins," the authors write. "The results of the current study provide the foundation for a large phase 3 clinical trial designed to assess the efficacy and safety of evacetrapib."

In an accompanying editorial, Christopher P. Cannon, M.D., of Brigham and Women's Hospital, Boston, comments on treatment strategies for low HDL-C levels.

"Current approaches to patients with low HDL-C levels are, first, institution of therapeutic lifestyle changes with diet and exercise and, if relevant, cessation of cigarette smoking. Each of these approaches has been shown to increase HDL-C and is associated with improved outcomes. The next step is to lower LDL-C. The current guidelines emphasize lowering LDL-C as the primary approach for patients with low HDL-C because it is a proven strategy, and the benefits of lowering LDL-C are present regardless of HDL-C levels (high or low). Next, in selected patients, some lipid experts use currently available therapies including niacin to increase HDL-C levels, although the evidence base for this approach is limited. Further interventions await data from the large randomized trials of current therapies (e.g., niacin) and emerging therapies like the CETP inhibitors, including dalcetrapib, anacetrapib, and, likely, evacetrapib. As such, the quest for the Holy Grail in coronary disease has many worthy knights on the trail."

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