Editorial

Effect of evacetrapib on cardiovascular outcomes in patients with high-risk cardiovascular disease

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Reducing serum low-density lipoprotein (LDL) cholesterol by statins has been shown to reduce cardiovascular events and mortality in secondary and primary prevention trials (1-3). Further reduction of serum LDL cholesterol in patients after an acute coronary syndrome treated with statins by ezetimibe (4) and in patients with cardiovascular disease treated with statins by the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor evolocumab (5) have been demonstrated to further reduce cardiovascular events .

Numerous epidemiological studies have demonstrated an inverse association between serum high-density lipoprotein (HDL) cholesterol levels and cardiovascular outcomes (6,7). However, randomized, placebo-controlled trials have not shown that increase of serum HDL cholesterol levels by drug therapy improves cardiovascular outcomes. In 3,414 patients with cardiovascular disease receiving intensive statin therapy randomized to receive niacin or placebo, at 2 years after therapy, niacin increased the median serum HDL cholesterol level from 35 to 42 mg/dL, reduced the serum LDL cholesterol level from 74 to 62 mg/dL, and reduced the serum triglyceride level from 164 to 122 mg/dL (8). At 3-year median follow-up, cardiovascular outcomes had occurred in 16.4% of patients treated with niacin versus 16.2% of patients treated with placebo (8). In 25,673 patients with cardiovascular disease treated with statin therapy randomized to 2 grams of extended-release niacin-laropiprant or placebo, at 3.9 years follow-up after therapy, compared with placebo, niacin-laropiprant increased serum HDL cholesterol by 6 mg/dL and reduced serum LDL cholesterol by 10 mg/dL (9). Compared with placebo, niacin-laropiprant did not reduce cardiovascular events but increased serious adverse events (9).

The cholesteryl ester transfer protein (CETP) inhibitors torcetrapib, dalcetrapib, evacetrapib, and anacetrapib inhibit the enzyme responsible for transferring cholesterol esters from HDL to very-low-density lipoprotein (VLDL) or LDL. These drugs have been shown to increase serum HDL cholesterol and reduce serum LDL cholesterol levels. However, at 15.1-year follow-up of 1,978 persons in the Framingham Heart Study, lower plasma CETP activity was associated with greater cardiovascular disease risk, which challenges the concept that CETP inhibition may lower cardiovascular disease risk (10). There are also conflicting data that genetic polymorphisms causing a lower mass or activity of CETP are associated with higher serum HDL cholesterol levels, lower serum LDL cholesterol levels, and a lower risk of coronary heart disease (11,12).

The Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) trial was a prospective randomized, double-blind study which randomized 15,067 patients, mean age 61.3 years, at high cardiovascular risk treated with atorvastatin to reduce the serum LDL cholesterol level to less than 100 mg/dL to receive torcetrapib 60 mg daily plus atorvastatin or atorvastatin only (13). At 12-month follow-up, torcetrapib increased serum HDL cholesterol 72.1%

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and reduced serum LDL cholesterol 24.9%. However, torcetrapib also increased systolic blood pressure by 5.4 mm Hg and caused a decrease in serum potassium and an increase in serum sodium, bicarbonate, and aldosterone levels. At a median follow-up of 550 days, the primary outcome of time to death from coronary heart disease, nonfatal myocardial infarction, stroke, or hospitalization for unstable angina pectoris was increased 25% (95% CI, 9% to 44%; P=0.001) by torcetrapib (13). Torcetrapib also increased all- cause mortality by 58% (95% CI, 1.14 to 2.19; P=0.006) (13). The off-target pharmacologic effects contributed to the increase in cardiovascular events and in all-cause mortality. It has also been suggested that CETP inhibition may cause HDL particles which are nonfunctional or even proatherogenic (14). Recent data showed that torcetrapib increased the HDL subclasses LpA-I and LpA-II equally and the apoC-III content of HDL without affecting the apoB-containing subclasses, supporting that the adverse effects of torcetrapib were not due to disturbances in lipoprotein transport (15).

The effects of dalcetrapib in patients with a recent acute coronary syndrome (dal-OUTCOMES) study randomized 15,871 patients, mean age 60.2 years, with a recent acute coronary syndrome to receive the CETP inhibitor dalcetrapib 600 mg daily or to receive placebo (16). Statins were used in 98% of patients at the time of randomization. At the time of randomization, the mean serum HDL cholesterol level was 42 mg/dL, and the mean serum LDL cholesterol level was 76 mg/dL. During the study, the serum HDL cholesterol level increased from baseline by 4% to 11% in the placebo group and by 31% to 40% in the group treated with dalcetrapib. Dalcetrapib caused a minimal effect on serum LDL cholesterol levels. Compared with placebo, dalcetrapib increased the median C-reactive protein level by 0.2 mg/L and the mean systolic blood pressure by 0.6 mmHg. At a median follow-up of 31 months, compared with placebo, dalcetrapib insignificantly increased the primary endpoint of death from coronary heart disease, nonfatal myocardial infarction, ischemic stroke, unstable angina pectoris, or cardiac arrest with resuscitation by 4% (16).

The Randomized Evaluation of the Effects of Anacetrapib through Lipid-modification (REVEAL) trial is an ongoing trial of 30,449 patients, mean age 67 years, with cardiovascular disease being treated with atorvastatin for an average of at least 4 years who were randomized to receive the CTEP inhibitor anacetrapib 100 mg daily or to receive placebo (17). At the time of randomization, the mean plasma HDL cholesterol was 40 mg/dL, and the mean plasma LDL level was 61 mg/dL. Results are anticipated in 2017 (17).

This editorial was written to discuss the results of the recently published paper on the Assessment of Clinical Effects of Cholesteryl Ester Protein Inhibition with Evacetrapib in Patients at a High Risk for Vascular Outcomes (ACCELERATE) trial (18). This study was a multicenter, randomized , double-blind, placebo-controlled phase3 trial which included 12,092 patients, mean age 64.9 years (46.5% men), who had at least one of the following medical conditions: an acute coronary syndrome within the prior 30 to 365 days (30.2%), cerebrovascular atherosclerotic disease (11.9%), peripheral vascular arterial disease (13.9%), or diabetes mellitus with coronary arterial disease (64.4%) (18). Statins were used to treat 96.5% of the patients. Antihypertensive drug therapy was used to treat 87.3% of the patients. The baseline serum HDL cholesterol level was 45.3 mg/dL, LDL cholesterol level was 81.4 mg/dL, and triglycerides was 128 mg/dL. The patients were randomized to receive evacetrapib 130 mg daily or to receive matching placebo. The primary efficacy endpoint was the first occurrence of any component of the composite of cardiovascular death, myocardial infarction, stroke, coronary revascularization, or hospitalization for angina pectoris. At 3 months, the mean serum HDL cholesterol was increased by 133.2% with evacetrapib and by 1.6% with placebo, and the mean serum LDL cholesterol level was reduced by 31.1 % with evacetrapib and increased by 6.0% with placebo. At a median follow-up of 26 months, a primary end point event occurred in 12.9% of patients treated with evacetrapib versus in 12.8% of patients treated with placebo (18).

These data demonstrated that evacetrapib significantly increased serum HDL cholesterol and significantly reduced serum LDL cholesterol. However, despite these favorable effects on serum HDL cholesterol and on serum LDL cholesterol, evacetrapib did not reduce cardiovascular events in patients with high-risk cardiovascular disease (18).

There is a large body of data from animal intervention studies and from human genetic studies supporting that CTEP inhibition is antiatherogenic and, therefore, will reduce cardiovascular events in humans (19). However, the lack of consistent data about the consequences of genetically defined CTEP deficiency, the variability in lipid parameters in patients treated with the different CETP inhibitors, and the negative clinical outcomes of the clinical trials reported support that lowering of CTEP will not reduce

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cardiovascular events (20).

The results from the ILLUMINATE trial (13), the dal-OUTCOMES trial (16), and the ACCELERATE trial (18) support that CTEP inhibition will not reduce cardiovascular events in humans. We are awaiting the clinical outcome data from the REVEAL trial to know whether or not the CETP inhibitor anacetrapib will reduce cardiovascular events.

Data from the niacin trials (8,9) and from the 3 completed large-scale CTEP inhibitor trials (13,16,18) have clearly demonstrated that raising serum HDL cholesterol does not improve cardiovascular outcomes. Future HDL cholesterol trials may need to measure HDL subclasses and HDL functionality (21). A low HDL cholesterol level may only be a marker of cardiovascular disease. Increasing HDL cholesterol so far by pharmacologic therapy has not been shown to reduce cardiovascular events. Although lowering serum LDL cholesterol by statins (1-3) ezetimibe (4), and the PCSK9 inhibitor evolocumab (5) have been demonstrated by large-scale clinical trials to reduce cardiovascular events, reducing serum LDL cholesterol by niacin (8,9), torcetrapib (13), and by evacetrapib (18) have not been shown to reduce cardiovascular events.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to disclose

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