The failure of clinical outcome trials with 3 different cholesteryl ester transfer protein (CETP) inhibitors has seriously compromised the hypothesis that CETP inhibition reduces atherosclerotic cardiovascular disease (ASCVD) risk. However, as outlined below, the hypothesis has still not been adequately tested and will die only if the ongoing Randomized Evaluation of the Effects of Anacetrapib Through Lipid-Modification (REVEAL) trial with the CETP inhibitor, anacetrapib, fails to deliver a positive result.

What Is CETP and What Does It Do?
CETP is present in the plasma of humans, nonhuman primates, rabbits, and hamsters but not in most other animal species.1 CETP promotes bidirectional transfers of cholesteryl esters and triglycerides between plasma lipoproteins in processes that result in an equilibration of these lipids between lipoprotein fractions. Because most of the cholesteryl esters in plasma are formed in high-density lipoproteins (HDLs) and because most triglyceride enters plasma as a component of very low–density lipoproteins or chylomicrons, the consequence of the equilibration promoted by CETP is a net mass transfer of cholesteryl esters from HDLs to potentially proatherogenic non–HDL fractions and a net mass transfer of triglyceride from triglyceride-rich very low–density lipoproteins and chylomicrons into HDLs and low-density lipoproteins (LDLs). Inhibition of CETP retains cholesteryl esters in the HDL fraction, which increases the concentration of HDL cholesterol and decreases the concentration of non-HDL cholesterol.

How Does CETP Affect ASCVD?
Human genetic studies support the proposition that CETP is proatherogenic and that its inhibition may reduce ASCVD risk. Large meta-analyses2,3 and large cohort studies4,5 have concluded that CETP gene polymorphisms associated with decreased CETP activity significantly lower the risk of having an ASCVD event. In the Copenhagen City Heart Study in which 10,261 people were followed for \( \leq 34 \) years, there were >3000 cardiovascular events and 3807 deaths. Two common CETP gene polymorphisms that reduce CETP activity were associated with significant reductions in the risk of ischemic heart disease, myocardial infarction, ischemic cerebrovascular disease, and ischemic stroke.4 Furthermore, the greater the number of affected alleles, the greater the impact on ASCVD risk. People with these polymorphisms also lived longer, with no evidence of adverse effects.4

What Are the Effects of Inhibiting CETP on Atherosclerosis in Animals?
In contrast to most animal species, rabbits have a high level of CETP activity in plasma. Also in contrast to most other animals, rabbits are extremely susceptible to development of diet-induced atherosclerosis. Inhibition of CETP in rabbits markedly reduces diet-induced atherosclerosis.6,7
supports the proposition that CETP inhibition should be antiatherogenic in humans.

### What Are the Effects of Inhibiting CETP on Plasma Lipids and HDL Function in Humans?

The effects of CETP inhibition in humans treated with torcetrapib, dalcetrapib, evacetrapib, anacetrapib, and TA-899512 on plasma lipids are summarized in the Table. All of these inhibitors increase the concentration of HDL cholesterol and apolipoprotein A-I. With the exception of dalcetrapib, they also reduce LDL cholesterol and apolipoprotein B levels. CETP inhibitors also reduce levels of the proatherogenic lipoprotein (a).

Effects of CETP inhibition on HDL function have also been investigated. HDLs isolated from people treated with torcetrapib, dalcetrapib, evacetrapib, anacetrapib, and TA-899512 have a normal or enhanced ability to efflux cholesterol from macrophages. Further evidence of preserved (or enhanced) HDL function was obtained from a post hoc analysis of the Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) trial in which the level of HDL cholesterol achieved in torcetrapib-treated patients remained as an inverse predictor of ASCVD events.

A similar conclusion was drawn from a post hoc analysis of the Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation (ILLUSTRATE) trial in which those who achieved the highest on-treatment HDL cholesterol level had significant regression of coronary atheroma.

### Torcetrapib

The effect of torcetrapib on clinical cardiovascular events was investigated in the ILLUMINATE trial that included 15,067 high-risk statin-treated patients. Torcetrapib increased HDL cholesterol levels by 72% and decreased LDL cholesterol levels by 25%. This trial was terminated after 18 months because of a statistically significant excess of deaths (93 versus 59) in those treated with torcetrapib. No single cause of death explained the harm caused by torcetrapib. There was also a significant 25% increase in ASCVD events in those taking torcetrapib.

The explanation for the harm caused by torcetrapib is not known but may have been the consequence of off-target adverse effects of the drug, including increased blood pressure, increased synthesis, secretion of aldosterone, and increased endothelin-1 levels in the artery wall.

### Dalcetrapib

The effect of dalcetrapib on clinical ASCVD events was investigated in the dal-OUTCOMES study that included 15,871 participants recruited soon after an acute coronary syndrome event. Treatment with dalcetrapib increased the concentration of HDL cholesterol by ≈30% but minimally affected LDL cholesterol and apoB levels. Treatment with dalcetrapib did not reduce ASCVD events.

The failure of the dal-OUTCOMES trial may have been because this agent did not reduce the level of LDL cholesterol. However, it may also have been because this trial was conducted in patients soon after an acute coronary syndrome event at a time when HDL function is compromised. This explanation was supported by the observation in the placebo group of the dal-OUTCOMES trial that, in marked contrast to the situation in people with stable ASCVD, the concentration of HDL cholesterol was unrelated to ASCVD events.

### Evacetrapib

The effect of evacetrapib on ASCVD events was evaluated in Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition With Evacetrapib in Patients at a High-Risk for Vascular Outcomes (ACCELERATE). Approximately 12,500 high-risk, statin-treated patients were randomized to receive evacetrapib or placebo with a predicted follow up of 3 years. The study was terminated after just over 2 years when it became apparent that there would not be a positive outcome if the trial continued to its planned 3-year follow-up. There was no evidence that evacetrapib caused harm. The reason for the failure is currently not known, but the trial may have been too short to detect benefit.

In many of the early statin trials conducted in people with existing ASCVD, the benefits of treatment were not apparent until well after 2 years of treatment. One example is the Cholesterol and Recurrent Events (CARE) trial that investigated effects of treatment with pravastatin in patients who had had a myocardial infarction. None of the participants had been treated with a statin before the trial. The level of LDL cholesterol at baseline was 139 mg/dL. Treatment with pravastatin reduced LDL cholesterol by 28% and after 5 years of treatment reduced fatal and nonfatal coronary heart disease events by 24%. However, after treatment with pravastatin for only 2 years (the time at which ACCELERATE was stopped), there was no effect on coronary heart disease events. If the CARE trial had been stopped at the same time 2-year time point as was the case with ACCELERATE, the conclusion...
would have been that statins do not reduce the risk of having a coronary heart disease event. If ACCELERATE had continued for 5 years (as was the case with all of the early statin trials), the result may well have been positive.

Anacetrapib

The Determining the Efficacy and Tolerability of CETP Inhibition With Anacetrapib (DEFINE) study was an 18-month trial designed to assess the lipid efficacy and safety of anacetrapib in high-risk, statin-treated patients (n=1623). Anacetrapib decreased the concentration of non-HDL cholesterol by 32% and increased HDL cholesterol by 138%. Anacetrapib had no effect on blood pressure or on levels of electrolytes or aldosterone. This trial was not powered to test the clinical outcome benefits of anacetrapib. It was concluded that treatment with anacetrapib had robust, favorable effects on levels of LDLs and HDLs, had an acceptable side-effect profile, and within the limits of the power of the study, did not have any of the adverse effects that were observed with torcetrapib.

The ongoing REVEAL trial (ClinicalTrials.gov number, NCT01252953) in which >30

Conclusions

There is compelling circumstantial evidence from human genetic studies and animal intervention studies that CETP is proatherogenic and that its inhibition will reduce ASCVD risk. However, randomized clinical outcome trials with 3 different CETP inhibitors have failed to show any reduction in ASCVD events. The possibility that these failures were caused by off-target effects of one of the drugs (torcetrapib) or trial design (dal-OUTCOMES and ACCELERATE) mean that the hypothesis that CETP inhibition will reduce ASCVD risk has still not been tested. Results of the REVEAL trial are awaited with great interest.

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