The Yin and Yang of Cholesteryl Ester Transfer Protein in Cardiovascular Disease

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Cholesteryl ester transfer protein (CETP) is a 79-kDa glycoprotein, present in humans, rabbits, primates, and hamsters but absent in rodents, dogs, horses, cows, and pigs, that facilitates transfer of cholesteryl ester from high-density lipoprotein (HDL) particles to low-density lipoprotein (LDL)–very-low-density lipoprotein (vLDL) particles in exchange for triglycerides, thereby participating in reverse cholesterol transport and regulating circulating HDL cholesterol (HDL-C) levels. In 1989, Brown et al described 2 Japanese subjects with markedly elevated HDL-C levels who were homozygous for a point mutation in the 5’-splice donor site of intron 14 of the CETP gene, a change that was shown to be incompatible with normal splicing of pre-messenger RNA. The following year, Inazu et al reported that 4 of 11 additional families from 3 different regions of Japan with elevated HDL-C were homozygous or heterozygous for the same mutation with gene-dose–dependent increases in HDL-C levels. Because epidemiological studies had generally shown an inverse relationship between circulating HDL-C levels and coronary heart disease (CHD), loss-of-function CETP mutations associated with increased HDL-C levels were thus thought to confer protection against CHD. This view is further supported by studies that have shown that increased CETP activity is associated with increased atherosclerosis progression and/or cardiovascular risk. A prospective 7-year follow-up study of American men of Japanese descent from the Honolulu Heart Program suggested that CETP mutations associated with reduced CETP activity and markedly elevated HDL-C (>60 mg/dL) may confer a lower risk of CHD, although an earlier cross-sectional analysis had suggested the opposite. Contrary to these observations, other studies have shown that reduced CETP activity is associated with paradoxically increased CHD despite elevated HDL-C levels. A deleterious CETP haplotype was shown to be associated with a 6-fold increase in myocardial infarction risk independent of HDL-C levels. Similarly, carriers of CETP Taq1B B2 allele were shown to have increased CHD events over a 10-year follow-up period. A recent meta-analysis involving subjects genotyped for 3 common CETP variants provided inconclusive results showing a very weak association between CETP deficiency and lower relative risk of CHD. Thus, the inconsistent and often contradictory relationship between CETP activity and CHD risk has created uncertainty as to whether CETP is a friend or foe in atherosclerosis.

In the present issue of Circulation, Vasan et al provide provocative data that add to this uncertainty. The authors evaluated 1978 initially asymptomatic subjects from the Framingham Heart Study, with a mean age of 51 years (54% women), in whom CETP activity was measured in blood samples obtained at baseline with the use of an accurate and reproducible fluorescent assay with an exogenous substrate. The authors report that baseline CETP activity was inversely related to future risk of cardiovascular events (including hard cardiovascular events) during a mean follow-up period of 15 years. The hazard ratio for cardiovascular events was 0.72 (P=0.004) for subjects with above-median CETP activity compared with those with below-median values. On multivariate analysis, this relationship remained significant after adjustments for several covariates, including age, sex, Framingham Risk Score, HDL-C, LDL cholesterol, triglycerides, and apolipoprotein B levels. The CETP activity showed a weak inverse correlation with HDL-C levels. The major strengths of this study are the large number of subjects, large number of cardiovascular events, relatively long follow-up period, and prospective nature of the study. The authors used a fabricated substrate to measure CETP activity, raising some concerns about whether activity measurements by this assay reflect in vivo activity; furthermore, CETP mass, measured in many prior studies, was not determined. Notwithstanding these potential concerns, this prospective observational study raises the tantalizing possibility that CETP activity is inversely related to cardiovascular risk and that such a relationship is unlikely to be mediated solely through a change in circulating HDL-C levels, because the correlation between CETP activity and HDL-C was meager, as has been shown by others.

Implications for CETP Inhibition as a Therapeutic Strategy

In view of the known inverse relationship between HDL-C levels and CHD, therapeutic inhibition of CETP activity has been considered a potential strategy for increasing HDL-C levels and reducing atherosclerosis. Experimental studies have generally shown favorable effects of CETP inhibitors on HDL-C and atherosclerosis in rabbits, a species with naturally high CETP activity, with the use of CETP antisense, CETP vaccine, and synthetic molecules like dalcetrapib and torcetrapib.
Similarly, in mice that normally lack CETP activity, overexpression of simian or human CETP increases atherosclerosis. These observations are tempered by contradictory findings in other studies, however. In the presence of prolonged hyperlipidemia, dalcetrapib failed to reduce atherosclerosis in rabbits, despite marked increases in HDL-C. Similarly, CETP overexpression was shown to reduce atherosclerosis in hypertriglyceridemic mice overexpressing apolipoprotein CIII and in SRB-1–deficient mice. Torcetrapib was recently shown to create a proinflammatory phenotype of atherosclerotic lesions and not to reduce atherosclerosis beyond atorvastatin in CETP-overexpressing mice. Torcetrapib was the first CETP inhibitor to advance to large-scale human trials. All human trials of torcetrapib were terminated in December 2006 when an interim analysis of the Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) trial by the Data Safety Monitoring Board showed that torcetrapib added to atorvastatin, compared with atorvastatin alone, significantly increased cardiovascular and noncardiovascular (infection and cancer) adverse events, including death, despite a 72% increase in HDL-C and 25% reduction in LDL cholesterol. Similarly, imaging trials failed to show a beneficial effect of torcetrapib on carotid and coronary atherosclerosis. Failure of torcetrapib has been attributed, at least in part, to non-CETP–dependent molecule-specific off-target effects, which include an increase in arterial pressure attributed to adrenal activation and increased aldosterone levels. One of the unexplained and interesting findings from the ILLUMINATE trial was an excess of deaths from cancer (24 versus 14) and infection (9 versus 0) in the torcetrapib arm, raising concerns about whether torcetrapib or CETP inhibition could interfere with innate immunity. Aside from the molecule-specific off-target toxicity of torcetrapib, it has also been suggested that cholesteryl ester–rich large HDL particles resulting from CETP inhibition are poor acceptors of free cholesterol from arterial wall macrophages because the ABCA-1 transporter selectively effluxes cholesterol to lipid-poor nascent apolipoprotein A-I–containing particles. This notion has been challenged by studies showing that macrophase ABCG-1, an alternative transporter, can effectively efflux cholesterol to large HDL particles and that HDL particles from human carriers of loss-of-function CETP mutation promote macrophage cholesterol efflux. The concept that HDL composition may influence HDL function is currently a topic of great interest, and several studies have suggested that an acute-phase response, hyperglycemia, exposure to mast cell–derived tryptase, or macrophage-derived myeloperoxidase may modify HDL composition, rendering it less functional or actually dysfunctional. Whether torcetrapib failed because it produced nonfunctional or dysfunctional HDL remains an intriguing but yet unproven possibility. At this time, therefore, it remains uncertain whether CETP has a net proatherogenic or atheroprotective role in humans. Ultimately, this question may be answered only when ongoing event-based randomized trials of alternative “clean” CETP inhibitors such as dalcetrapib and anacetrapib, which to date appear to not have off-target adverse effects on blood pressure, aldosterone, or other aspects of adrenal function, are completed. It is conceivable that a potent inhibitor of CETP could produce large increases in HDL levels, which may produce atheroprotective effects if the beneficial vascular effects of HDL increase are not neutralized by adverse off-target effects. Historical precedent suggests that failure of a first-in-class drug does not always sound a death knell for the entire class.

**Disclosures**

The author is a member of the Steering Committee for the dal-Outcome study, which is a randomized double-blind, placebo-controlled clinical trial investigating the effects of dalcetrapib on cardiovascular events in patients after an acute coronary syndrome.

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