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EDITORIAL COMMENT

Is the Cholesteryl Ester Transfer Protein Proatherogenic or Antiatherogenic in Humans?*

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The strong inverse association of plasma levels of high-density lipoprotein cholesterol (HDL-C) with coronary heart disease (CHD) has long tantalized the preventive cardiovascular medicine community with the prospect of new therapies that raise levels of HDL-C and thus reduce the risk of CHD. The finding that markedly elevated HDL-C levels are caused by genetic deficiency of the cholesteryl ester transfer protein (CETP) and, subsequently, that pharmacologic inhibition of CETP substantially raises levels of HDL-C in humans only served to promote the anticipation of a major new therapeutic breakthrough in the prevention of CHD. However, this concept suffered a substantial blow with the demise of the CETP inhibitor torcetrapib in December 2006 due to a 60% increase in mortality in the actively treated group of a large outcome trial called ILLUMINATE (Investigation of Lipid Level management to Understand its iMpact IN ATherosclerotic Events) (1). Further disappointment came from the results of atherosclerosis imaging trials indicating no significant effects on progression of coronary atherosclerosis or carotid intimal medial thickness (IMT) despite increases of HDL-C of >50% (2,3) Importantly, however, torcetrapib raises blood pressure in some individuals through a mechanism unrelated to CETP inhibition, and therefore it is unclear whether the disappointing results with torcetrapib are due to inhibition of CETP or to off-target effects of the drug (4). The question of whether CETP is pro- or antiatherogenic, and therefore whether inhibition of CETP using a different inhibitor might be beneficial, is critically important not only to the concept of whether CETP inhibition is still a viable approach, but also to the broader issue of targeting HDL-C therapeutically.

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Cholesteryl ester transfer protein mediates the transfer of cholesteryl esters (CE) from HDL to apolipoprotein (apo) B-containing triglyceride-enriched remnant lipoproteins in exchange for triglycerides. After acquiring HDL-derived CE, apoB-containing lipoproteins can then be cleared by the low-density lipoprotein (LDL) receptors in the liver. This pathway has been proposed as the major pathway in humans by which HDL-derived cholesterol is transported back to the liver (5), and studies in mice engineered to express CETP support this concept (6). Furthermore, triglyceride-enriched HDL are a good substrate for hepatic lipase, which, via its action on HDL, may favor the production of lipid-poor apoA-I (7), a major acceptor of cholesterol efflux. Thus, it is theoretically possible that reduced levels of CETP activity could result in reduced reverse cholesterol transport due both to reduced generation of lipid-poor apoA-I as well as to reduced rate of return of HDL-derived cholesterol to the liver for excretion. This concept, coupled with the torcetrapib experience, makes it imperative to discern the true relationship between CETP and atherogenesis in humans.

This has been a central question ever since the discovery of CETP deficiency as a cause of elevated HDL-C levels, and, surprisingly, it remains unanswered. Studies in the relatively small number of homozygous CETP-deficient subjects in Japan have suggested either increased or decreased risk of CHD (8,9) and this issue is still debated. Studies of heterozygous CETP-deficient subjects in the Honolulu Heart Study have not been definitive either (10). Similarly, studies investigating the association between common variants in the human CETP gene and cardiovascular disease have yielded contradictory results despite consistent associations with HDL-C levels (11). Thus, genetic studies have not answered the question of the relationship of CETP to atherosclerosis.

Studies that focus on the association between plasma CETP protein mass levels and CHD outcomes may have the potential to clarify this issue, but relatively few studies have been published and they do not provide a consistent message. Higher CETP protein levels were associated with prevalent CHD (12), faster progression of angiographic CAD (13), faster progression of carotid IMT (14), and greater risk of incident CHD events in a nested case-control study within the EPIC (European Prospective Investigation Into Cancer and Nutrition)-Norfolk study (15). However, no differences in CETP protein levels were observed in a small study of patients undergoing coronary angiography (16) and in a nested case-control study within the PREVEND (Prevention of Renal and Vascular End-Stage

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Disease) study (17). Finally, lower CETP protein levels were found to be associated with increased CHD events in a prospective study of patients treated with a statin (18). It is possible that these discrepant results are due to confounding factors that may alter the relationship between CETP protein levels and CHD outcomes. For example, the positive association between CETP protein levels and CHD events in the EPIC-Norfolk study was restricted to those subjects with higher triglyceride levels (15). In contrast, in the PREVEND study, lower CETP protein levels were predictive of increased CHD events only in the subjects with lower triglycerides (19).

The role of CETP in influencing atherogenesis is in turn influenced by the metabolic milieu in which CETP operates. Low-density lipoprotein cholesterol and triglyceride levels, lifestyle habits such as smoking and alcohol use, and drugs such as statins have all been shown to affect plasma CETP activity. Measures of CETP activity may therefore be more informative than those of CETP protein mass, but assays are not standardized and are cumbersome to perform in the large numbers required in observational studies. In a small study of subjects undergoing coronary angiography, higher CETP activity was found in subjects with angiographic coronary disease compared with controls (20). More recently, a significant positive association between CETP activity and carotid IMT was found in both diabetic and nondiabetic subjects (21). Given the relative paucity of data, the article by Zeller et al. (22) in this issue of the *Journal* is a welcome addition to the literature. This paper reports the results obtained in a study evaluating plasma CETP activity and protein levels in sequential subjects admitted with first myocardial infarction. Subjects in the highest tertile of CETP activity had statistically higher CETP protein levels, total cholesterol, LDL-C, non–HDL-C, and triglycerides, had lower HDL-C, had a higher percentage of smokers, and were also significantly younger. A multiple linear regression analysis indicated that the younger age of the subjects with higher CETP activity was independent of other potentially confounding risk factors, suggesting that higher CETP activity is an independent risk factor for early myocardial infarction. The focus on CETP activity in this study is commendable. However, measuring CETP activity has some limitations that need to be considered. Zeller et al. (22) measured CETP activity by using a method that is very dependent on the concentration of endogenous apoB-containing lipoproteins as acceptor particles, which themselves are highly atherogenic. In this context, elevated CETP activity could be a surrogate for elevated levels of remnant lipoproteins; indeed, upon multivariate analysis, non–HDL-C levels were an independent predictor of CETP activity. Thus it remains uncertain whether the elevated CETP activity is causal or simply a sophisticated biomarker for a more atherogenic lipoprotein profile. Nevertheless, these results generally support a proatherosclerotic role of CETP.

In light of the importance of this question, further studies that carefully assess the relationship of plasma CETP protein mass and activity to CHD in the context of a carefully defined metabolic milieu and controlling for detailed measures of atherogenic lipoproteins are still needed and may be important in helping to determine the future of CETP inhibition as a therapeutic strategy.

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