HDL-cholesterol levels and cardiovascular risk: acCETPing the context

Richard A. Lange and Merry L. Lindsey*

Medicine/Cardiology, University of Texas Health Science Center, San Antonio, TX 78229, USA

Online publish-ahead-of-print 28 October 2008

This editorial refers to 'CETP genotype predicts increased mortality in statin-treated men with proven cardiovascular disease: an adverse pharmacogenetic interaction'† by J.J. Regieli et al., on page 2792

High levels of plasma high-density lipoprotein cholesterol (HDL-C) are associated with a decreased risk of cardiovascular disease. Cholesterol ester transfer protein (CETP) facilitates the transfer of cholesteryl esters from HDL to triglyceride-rich lipoproteins, and its inhibition raises HDL-C levels. Accordingly, interest has focused on CETP inhibition to augment current lipid-lowering strategies.

In a substudy from the Regression Growth Evaluation Statin Study (REGRESS) angiographic trial cohort,1 Regieli and colleagues evaluated 812 statin-treated participants and found that the 60% who were carriers of the TaqIB-B2 CETP gene allele had ~20% lower CETP and 15% higher HDL-C serum concentrations than those without the allele, and a markedly increased risk of atherosclerotic disease mortality. The hazard ratio per each B2 copy was 1.60 (P = 0.01). The authors concluded that statin use in the setting of low CETP levels worsens clinical outcome in patients with proven cardiovascular disease. In light of the Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) trial—which showed a 61% increase in combined mortality and cardiovascular events in 15 000 individuals at high risk for coronary events who were treated with atorvastatin plus torcetrapib, a CETP inhibitor, compared with atorvastatin alone2—the Regieli study highlights the fact that much remains unknown about the interaction between HDL-C metabolism and cardiovascular disease.

CETP is a plasma glycoprotein that shuttles cholesteryl esters, phospholipids, and triglycerides between HDL-C, very low-density lipoprotein and low-density lipoprotein (LDL). CETP genotypes that result in moderate inhibition of CETP activity are associated with increased serum HDL-C levels and reduced coronary risk. In contrast, pharmacological CETP inhibition has not proven to be clinically beneficial. In statin-treated patients, concomitant CETP inhibition with torcetrapib did not slow the progression of atherosclerosis3,4 and was associated with a 25% increase in cardiovascular events and 58% increase in mortality, despite increased HDL-C levels. Although this increase in events has been attributed to the ‘off-target’ effects of torcetrapib (i.e. increased systemic arterial pressure and serum aldosterone), the possibility remains that combination statin and CETP inhibition therapy is harmful. There are several possible mechanisms that may account for the negative outcomes.

While CETP synthesis is generally assigned to liver and adipose tissue, many organs express CETP mRNA, including spleen, bone marrow, adrenal gland, intestine, kidney, lung, prostate, brain, heart, and skeletal muscle. Apart from its role in regulating HDL-C, CETP may be an important anti-inflammatory mediator. For example, overexpressing human CETP in transgenic mice increases their survival rate following endotoxin exposure, attenuates the associated tumour necrosis factor-α and interleukin-6 responses, and enhances endotoxin binding to HDL-C to increase its clearance via the liver.5 Thus, CETP may play a role in the regulation of cytokines and inflammation. Interestingly, in the ILLUMINATE trial, CETP inhibition with torcetrapib was associated with increased serum C-reactive protein levels and a 2-fold increased incidence of death from non-cardiovascular causes, primarily from infection and cancer.

Although CETP inhibition increases serum HDL-C levels, the resultant particle may be dysfunctional or even pro-atherogenic.6 Pharmacological inhibition of CETP increases the levels of a larger, less dense HDL-C (so called, HDL3), which may be less effective in mediating reverse cholesterol transport than the small, more dense HDL1 particle. Furthermore, oxidation of ‘quiescent’ HDL particles or an increase in the ‘pro-atherogenic’ apolipoprotein A-II component of HDL-C as a consequence of CETP inhibition may render them pro-inflammatory.6

While the current study demonstrates that the B2 CETP gene allele is associated with increased mortality in comparison with

* Corresponding author. Tel: +1 210 567 4673, Fax: +1 210 567 6960; Email: lindseym@uthscsa.edu
† doi:10.1093/eurheartj/ehn450
1 doi:10.1093/eurheartj/ehn465

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2008. For permissions please email: journals.permissions@oxfordjournals.org
the B1 allele, it suggests but does not prove that ‘the efficacy of statin therapy to reduce cardiovascular risk depends on CETP genotype’ as the authors conclude. Since all patients in the study received statin therapy, the association of CETP genotype and response to statin therapy cannot be determined without no-statin control groups. The suggestion that statin therapy in the setting of low CETP levels is associated with increased mortality, however, is not without merit. This issue remains controversial. Several published studies failed to show that the CETP variant influences the response to statin therapy, one of which was authored by several investigators of the current study. The reason for the varying results may relate to differences in (i) study design; (ii) the types of study patients enrolled; (iii) medication compliance; or (iv) duration of follow-up. It does not, however, appear to be related to differences in the percentage of patients in each study treated with a statin, as proposed by Regieli and co-workers; when the statin-treated patients within each study are assessed, the TaqIB genotype was not associated with coronary artery disease risk.

It is important to note that the study by Regieli et al. included no diabetic patients and exclusively evaluated men. Thus, whether their observations extend to diabetic patients or women requires additional investigation. CETP transfers oestriol esters from HDL-C to LDL, where it may serve an anti-oxidant role. Whether CETP genotypes influence this transfer to modify the cardiovascular risk still needs to be determined.

In summary, the study by Regieli et al. uses a pharmacogenomic approach to suggest an interaction between statin therapy and CETP genotype. A pharmacogenomic approach has proven clinically useful in predicting the anti-coagulation response to warfarin therapy and the risk of statin-induced myopathy. However, before CETP genotyping is utilized to decide which patients should receive statin therapy, the results of the current study require confirmation in a properly performed, appropriately powered, prospective study inclusive of both placebo-treated and statin-treated patients with genotypes reflective of the general population. In addition, future studies are needed to uncover the mechanisms and circumstances whereby CETP inhibition—due to genetic variation or pharmacological manipulation—may increase cardiac risk despite favourable changes in HDL-C levels.

Conflict of interest: none declared.

Acknowledgements
The authors acknowledge grant support from NIH HL75360 and AHA 0855119F (M.L.L.).

References
5. Cazita PM, Barberio DF, Moretti AI, Quintao EC, Soriano FG. Human CETP expression enhances the mouse survival rate in an experimental systemic inflammation model: a novel role for CETP. Shock 2008; in press.