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OPINION ARTICLE

CETP inhibitors and cardiovascular disease: Time to think again [version 1; peer review: 2 approved]

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Abstract

Inhibition of cholesteryl ester transfer protein (CETP) lowers plasma low-density lipoprotein cholesterol concentration and raises high-density lipoprotein (HDL) cholesterol, suggesting it might prevent cardiovascular disease (CVD). From the outset, however, the concept has been controversial owing to uncertainty about its effects on HDL function and reverse cholesterol transport (RCT). Although there has long been good evidence that CETP inhibition reduces atherosclerosis in rabbits, the first information on CETP as a CVD risk factor in a prospectively followed cohort was not published until after the first Phase 3 trial of a CETP inhibitor had begun. The worrying finding that CVD incidence was related inversely to plasma CETP has since been reproduced in each of five further prospective cohort studies. Similar results were obtained in subjects on or off statin therapy, for first and second CVD events, and for mortality as well as CVD morbidity. Additionally, two recent studies have found alleles of the *CETP* gene that lower hepatic CETP secretion to be associated with an increased risk of myocardial infarction. Meanwhile, *CETP* gene transfer in mice was found to increase RCT from peripheral macrophages *in vivo*, and human plasma with high CETP activity was shown to have a greater capacity to remove cholesterol from cultured cells than plasma with low activity. This mounting evidence for a protective function of CETP has been given remarkably little attention, and indeed was not mentioned in several recent reviews. It appears to show that CETP inhibition does not test the HDL hypothesis as originally hoped, and raises a pressing ethical issue regarding two Phase 3 trials of inhibitors, involving more than forty thousand subjects, which are currently in progress. As the weight of evidence now clearly supports an adverse effect of CETP inhibition on CVD, an urgent review is needed to determine if these trials should be discontinued.

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Background

Cholesteryl ester transfer protein (CETP) is a hydrophobic glycoprotein in plasma that catalyzes the transfer of neutral lipids between plasma lipoproteins¹. The notion that inhibition of CETP activity might prevent coronary heart disease (CHD) was based on the knowledge that it both reduces plasma low-density lipoprotein (LDL) cholesterol concentration, and raises high-density lipoprotein (HDL) cholesterol. While there is abundant evidence that reduction of LDL cholesterol is likely to be beneficial, the effect of CETP inhibition on the function of HDL in reverse cholesterol transport from tissues (RCT) has been uncertain.

In 1996 Fielding and Havel² argued against a hasty commitment to CETP inhibitors, drawing attention to evidence that CETP participates in the remodelling of the cholesteryl ester-rich α -HDLs that generates the small lipid-poor pre β -HDLs that are the primary acceptors of cholesterol via the ABCA1 transporters in cell membranes³. The rise in HDL cholesterol might be misleading, they argued, and reflect only retention of cholesteryl esters in the particles, while the uptake of cholesterol from arterial cells is diminished. Nevertheless, encouraged by reports that *CETP* gene transfer induced atherosclerosis in mice⁴ and that CETP inhibition prevented atherosclerosis in rabbits⁵⁻⁷, drug discovery programmes made rapid progress.

The case for inhibition was weakened when later studies of CETP transgenic mice contradicted the earlier findings^{8,9}, and the incidence of CHD was not found to be significantly reduced in familial CETP deficiency¹⁰. Studies of the relation of CHD to single nucleotide polymorphisms (SNPs) of the *CETP* gene yielded disparate outcomes, which were not resolved by meta-analyses¹¹⁻¹³. When Dullaart *et al.*¹³ meta-analyzed data on the *Taq1B* SNP (rs708272) from population-based and high-risk groups separately, the odds ratio for cardiovascular disease (CVD) in homozygotes for the *B2* allele (who have low CETP activity) was 0.84 in the high-risk subjects, but 1.45 in the population-based samples. This suggested that low CETP activity actually increases CVD risk, and that its seeming protective effect in some studies may have resulted from selection towards a lower frequency of the *B2* allele in high-risk groups.

The dual uncertainties over the effect of CETP inhibition on HDL function and whether it is more likely to reduce or increase CVD in humans were unresolved when the first Phase 3 study (ILLUMINATE; NCT00134264) of a member of this class of drugs (torcetrapib) was started in July 2004¹⁴. In June 2007, the trial was terminated after it had become clear that the treatment had increased the incidence of the primary CVD endpoint. The authors concluded that this was probably owing to an unanticipated rise in blood pressure, but three findings challenged this interpretation. CHD mortality was related inversely to increment in blood pressure; the incidence of stroke was not raised by treatment; and non-cardiovascular mortality was increased. A Phase 3 trial of dalcetrapib (Dal-OUTCOMES; NCT00658515), a less potent inhibitor with little or no effect on blood pressure, was started in April 2008. In November 2012, this study was also terminated when it became evident that the outcome was not going to be positive¹⁵.

In the same year that ILLUMINATE enrolled its first participant, the first prospective data on plasma CETP as a risk factor for clinical

CVD events were also published. Boekholdt *et al.*¹⁶ had found that CETP concentration, with which CETP activity is linearly related¹⁷, did not differ significantly between 1,400 controls and 735 subjects who had developed myocardial infarction (MI) during six years of follow-up, although a positive association was seen on *post hoc* analysis in subjects with plasma triglycerides exceeding the median of 1.7 mmol/l.

Recent findings on plasma CETP as a CVD risk factor

The first prospective observational cohort study of plasma CETP activity or concentration as a risk factor for clinical CVD events did not appear until July 2006, two years after ILLUMINATE had started. Since then five further similar studies have been published. All six studies found CVD incidence to be related *inversely* to plasma CETP¹⁸⁻²³. The designs and results of these studies are summarised in Table 1. Cohorts ranged from 1,002 to 3,256 subjects, and follow-up periods from two to 15 years (weighted average, 7.6 years). One study followed men and women separately²³. Three were of first CVD events in healthy subjects^{18,19,23}; two were of second events in subjects with an existing history of CHD^{20,21}; and in one study primary and secondary events were pooled²². In two studies that looked at mortality in addition to CVD morbidity^{21,22} this was also negatively associated with CETP. Results in subjects taking pravastatin or atorvastatin^{18,20} mirrored those in other subjects. The suggestion in the earlier case-control study¹⁶ that subjects with raised triglycerides might differ from others was not confirmed.

Recent genome-wide analyses of CETP alleles and CVD

The *CETP* gene has been mapped to locus 16q21. It spans about 25 kb, and consists of 16 exons and 15 introns. In the absence of a clear picture from candidate gene studies of the association of SNPs with CVD, two genome-wide analyses have recently been published, whose results appeared to conflict with those of the observational epidemiology. In a study of more than 350,000 SNPs in 18,245 women followed for 10 years, Ridker *et al.*²⁴ observed that three SNPs in or around the *CETP* gene (rs708272, rs4329913, rs7202364) were associated with increased HDL cholesterol and a reduced incidence of MI. A subsequent Mendelian randomization analysis found a single SNP of *CETP* (rs3764261) to be associated with raised HDL cholesterol and an apparent four per cent reduction in the incidence of MI²⁵.

Reconciling the observational epidemiology and genome-wide analyses

The reliability of prospective observational epidemiology for the identification of causal effects in complex diseases has been in the spotlight of late, after some results were not confirmed in randomized clinical trials. Could the results of the recent observational studies of CETP be another instance of confounding or reverse causation? Confounding seems unlikely as multivariate analyses found the relation between CVD events and CETP concentration or activity to be independent of age, gender, hypertension, body mass index, plasma triglycerides, adiponectin, diabetes, and smoking habit¹⁸⁻²³. Reverse causation due to a reduction of plasma CETP in response to vascular inflammation also seems improbable, as the association persisted after adjustment for plasma homocysteine, interleukin-6 and C-reactive protein concentrations^{22,23}.

As discussed by several authors²⁶⁻²⁸, genome-wide analyses are also not without their limitations, and several aspects of the two studies

Table 1. Prospective observational cohort studies of CVD risk and plasma CETP concentration or activity.

Study	Design	Results
Marschang 2006 ¹⁸	1002 subjects (mean age, 65 yr; 44% female) free of CVD and taking pravastatin were followed for two years, during which 100 suffered a CVD event.	Significantly more CVD events in the bottom quartile of CETP conc than in the top quartile (OR 3.2, P=0.001). The association remained significant (P=0.001) after adjustment for age, sex, lipids and other risk factors. Similar result observed for cardiac events alone (P=0.009).
Vasan 2009 ¹⁹ Framingham Heart Study	1978 subjects free of CVD (mean age, 51 yr, 54% female) were followed for 15 years, during which 320 suffered a CVD event.	CVD incidence was negatively associated with CETP activity (P=0.004) after adjustment for age, sex and standard risk factors. CETP activity $\geq$ median was associated with a risk reduction of 30%.
Khera 2010 ²⁰ PROVE IT-TIMI 22 Study	3218 subjects (mean age, 58 yr; 21% female) with clinical CHD taking either atorvastatin or pravastatin were followed for two years, during which 150 suffered a recurrent AMI or CHD death.	CETP conc was negatively associated with CHD risk in unadjusted data (HR per SD increase 0.77, P=0.005) and after adjustment for age, sex and other risk factors (0.81, P=0.027). In subjects whose LDL was below the median, CETP conc above the median was associated with a HR of 0.52 (P=0.02).
Duwnsee 2010 ²¹ KAROLA Study	1132 subjects with clinical CHD (mean age 59 yr, 15% female, 18% diabetics) were followed for 8 yr, during which there were 150 cases of fatal or non-fatal CVD, and 119 deaths.	With or without adjustment for sex, age and standard risk factors, HR for a new CVD event was negatively associated with CETP conc. Relative to subjects with CETP above the median, those below it had a HR for CVD of 1.84 (P<0.02), and for total mortality of 1.57 (P=0.04).
Ritsch 2010 ²² LURIC Study	3256 subjects referred for coronary angiography (mean age 62 yr, 30% female), of whom 2560 had verified CAD, were followed for a mean of eight years, during which there were 754 total deaths, and 474 deaths from CVD.	CETP conc was lower in patients with CAD than in those without (P=0.002). Relative to the top CETP quartile, age- and sex-adjusted HR for CVD death in the bottom quartile was 1.38 (P=0.02), and that for total mortality was 1.37 (P=0.004). HRs were unaffected by adjustment for other risk factors.
Robins 2013 ²³ Framingham Offspring Study	2679 subjects (mean age, 58 yr, 56% female) free of CVD were followed for a mean of 10.4 yr, during which 187 suffered a CVD event.	In men CVD risk was associated negatively with CETP activity and positively with PLTP activity. After adjustment for PLTP and other risk factors, CVD remained negatively associated with CETP activity (HR 0.64, P=0.026). No significant associations in women.

Studies limited to coronary angiography without clinical endpoints are not included. AMI, acute myocardial infarction; BMI, body mass index; CAD, coronary artery disease; CHD, coronary heart disease; CVD, cardiovascular disease; HR, hazard ratio; OR, odds ratio; PLTP, phospholipid transfer protein.

warrant consideration. One is that there appears to have been no concordance between them in the alleles found to be associated with MI. Second, as data on plasma CETP were not available to either study, the relations with disease could have been owing to linkage with other genes that affect HDL and MI through independent mechanisms. The strongest association in the first study²⁴ was with rs708272, the *Taq1B* SNP of *CETP*. This intronic polymorphism has no direct affect on CETP activity. Furthermore, the allele associated with low incidence of MI has also been found to be associated with a low prevalence of metabolic syndrome²⁹, a potential confounder being itself a strong risk factor for CVD. The other two alleles were remote from the *CETP* gene, being in *SLC12A3* and *NUP93*, respectively a solute transporter gene and the gene for a nucleoporin. The relation of MI to rs3764261 described in the more recent genome-wide study was adjusted for age and sex, but not for other potential confounders²⁵. Furthermore, the result has since been contradicted by a meta-analysis of data from 16,570 subjects³⁰, which found the *T* allele of the same SNP to be associated with reduced effectiveness of statins in preventing MI.

Papp *et al.*³¹ have recently addressed the issue of genetically determined low CETP activity by using mRNA allelic expression and splice isoform assays to identify genetic variants that affect plasma CETP concentration, and then examining their relation to incident MI. In studies of 94 human livers, a common alternatively spliced isoform lacking exon 9 prevented CETP secretion in a

dominant-negative manner. Increased formation of this isoform was exclusively associated with two polymorphisms in high linkage disequilibrium: one in exon 9 of *CETP* (*rs5883-C>T*), which alters an exonic splicing enhancer sequence, and another in intron 8 (*rs9930761-T>C*), which changes a splicing branch point nucleotide. In the INVEST-GENES prospectively followed cohort, it was found that rs5883T/rs9930761C were associated with high incidence rates of MI and stroke ($P = 0.005$) despite raised HDL cholesterol, strongly reinforcing the observational epidemiology.

Recent studies of CETP, HDL function and reverse cholesterol transport

While the epidemiologic landscape has thus evolved, laboratory research has strengthened the evidence that CETP plays an important role in RCT. Tanigawa *et al.*³² found that hepatic *CETP* gene transfer in mice stimulated the transport of cholesterol from peritoneal macrophages to the liver, followed by its elimination as bile acids. Tchoua *et al.*³³ independently confirmed this result, and showed that the effect was blocked when the animals were given torcetrapib. There is no accepted method for quantifying reverse cholesterol transport *in vivo* in humans, but three groups have recently reported that human plasma with high CETP activity had a greater capacity to promote cholesterol efflux from cultured cells than plasma with low activity^{34–36}. Villard *et al.*³⁴ showed further that addition of purified CETP increased both the pre β -HDL concentration in normal human plasma and its capacity to remove cholesterol

from cultured cells, reproducing an earlier result obtained with plasma from a subject with familial CETP deficiency³⁷. Thus, the confusion over the contribution of CETP to RCT appears to have been resolved, and the concerns expressed by Fielding and Havel almost 20 years ago substantiated.

Perspective

The history of the hypothesis that CETP inhibition will prevent atherosclerosis can be summarised thus. At the outset, our understanding of HDL biochemistry did not permit any predictions of its effect on RCT, but was sufficient to tell us that it might go either way. In the absence of information on the relation of CVD risk to CETP activity in humans, enthusiasm for the concept was fuelled by positive results in cholesterol-fed rabbits, which seemed to confirm that a rise in HDL cholesterol is a dependable biomarker of benefit. However, the first prospective cohort study of CETP as a CVD risk factor challenged this assumption. Since then, five further prospective observational studies have left no doubt that in populations CVD risk is related inversely to CETP activity. Confounding and reverse causation seem unlikely explanations. Although two genome-wide analyses appeared to have produced contrary evidence, for the reasons discussed they have not refuted the observational data. On the other hand, the latter have been reinforced by reports that subjects with functional *CETP* alleles that lower CETP secretion have an increased risk of MI. Thus, the weight of evidence has now shifted to the likelihood that CETP inhibition will have an adverse effect on CVD outcomes, not the beneficial effect that was hoped for. Recent laboratory studies on the impact of CETP activity on the cholesterol transport function of HDL have been consistent with this interpretation.

This interpretation does not conflict with the anti-atherogenic effect of CETP inhibition in rabbits. Apart from the obvious possibility of a species specific difference in cholesteryl ester dynamics, Shimoji *et al.*³⁸ reported that dalcetrapib increases the synthesis rate of the major HDL protein (apo AI) in rabbits by 44 per cent, an effect that on its own would be expected to substantially reduce atherosclerosis³⁹. By contrast, inhibition of CETP with torcetrapib had no effect on apo AI synthesis in humans⁴⁰. It is also worth noting that probucol, which increases CETP activity⁴¹, also prevents atherosclerosis in rabbits despite lowering apo AI synthesis rate^{41,42}.

Although the body of disquieting data has been growing for several years, there has been surprisingly little public discussion of the issue. The paper describing the outcome of ILLUMINATE¹⁴ made no reference to the results of Marschang *et al.*¹⁸ published the year before. Likewise, the report on Dal-OUTCOMES¹⁵ made no mention of any one of the six observational cohort studies listed in Table 1, all of which were already in print. The same is true of an article investigating the harm caused by torcetrapib in ILLUMINATE⁴³, and of several recent review articles^{44–48}.

Implications

These recent developments have significant implications. First, they are consistent with other evidence that plasma HDL cholesterol

concentration is not a reliable marker of the efficiency of RCT^{49,50}. Second, they show that clinical trials of CETP inhibitors do not test the HDL hypothesis in the manner originally envisaged. Third, they raise a pressing issue in the context of two Phase 3 studies of second generation CETP inhibitors currently in progress. ACCELERATE (NCT01687998)⁵¹, which began in 2012 and is expected to finish in 2016, has enrolled about 12,000 patients with high-risk CVD to assess the efficacy of evacetrapib⁵² in preventing CVD events. REVEAL (NCT01252953)⁵³, commenced in 2011 and expected to be completed in 2017, has enrolled 30,624 patients for a similar study of anacetrapib⁵⁴. In both studies, the patients in each arm are being given a statin to control LDL concentration prior to randomization.

Anacetrapib is the most potent CETP inhibitor to date, and was found in DEFINE (NCT00685776)⁵⁴ to lower LDL cholesterol by 50 per cent compared with the 25 per cent achieved with torcetrapib¹⁴. It is theoretically possible that this greater impact on LDL will override any adverse effect on HDL function, but it is equally possible that its greater impact on HDL cholesterol (140 per cent increase compared with 70 per cent) reflects such an extreme disturbance of HDL metabolism that its consequences will predominate. Neither the prospective epidemiology nor studies of familial CETP deficiency have provided evidence of a fall in CVD risk at extremely low activities. Although DEFINE recorded no increase in CVD in patients given anacetrapib, the authors noted that the study was too small to provide reliable information on clinical events⁵⁴.

Conclusion

Given that the tide of evidence has turned so strongly against CETP inhibition in recent years, the question must be asked of whether it is now ethical to continue with the two Phase 3 trials in progress. A clinical trial is considered to be ethical only if it has a sound scientific basis and a favourable risk-benefit balance⁵⁵. The two trials in question no longer satisfy either requirement, as there is clearly a strong possibility that the drugs will have exactly the opposite effect on CVD to that intended. Some might argue that there is no cause for concern, as morbidity and mortality are being regularly reviewed by data monitoring committees. However, such committees can intervene only when pre-specified statistical criteria have been met, by which time many participants may have suffered harm.

Carrying on and hoping for the best is not an acceptable option. An independent review is urgently needed to determine if the trials should be discontinued.

Competing interests

No competing interests were disclosed.

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Cesare Sirtori

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This paper by Miller attempts to elucidate once and for all the present role of CETP and CETP antagonists in coronary prevention. The message is clear and well written. I do have a question on the structure of the paper however: while the background of CETP from the earlier papers by Havel is clear and well written, I question the idea of separating this from the very informative Table 1 which collates two separate pieces of information and is otherwise unclear.

Also, as the current trend is to evaluate genomic analysis, in particular by Mendelian randomization, this could indicate that HDL is not a genetic risk component. This should be given special emphasis, since the Mendelian randomization analysis was focused on LIPC (just one determinant of HDL levels) whereas the author points out that SNPs of CETP are also probably involved. However he gives no explanation of the mechanism of these SNPs, which are apparently associated with raised HDL and also with reduced incidence of MI.

In my view, the major focus of this paper should be on drugs, especially as drugs are still used to antagonize CETP in clinical trials. In the studies on torcetrapib it was noted ([Nicholls et al, Circulation 2008](#)) that individuals with the highest post-treatment HDL-cholesterol are apparently protected from coronary disease. Does this make sense? After all if HDL is traveling through the blood in very large amounts without going back to the artery this could provide some potential protection, although this should be evaluated with more rigor. A final note on the studies with torcetrapib is the incremental elevation of blood pressure. The rise of blood pressure was of such little entity (at most 5 mmHg) that just posting these data in a risk score (Framingham or other) allowed one to conclude that this influences risk minimally and does not modify the enormous change in risk consequent to the HDL rise elicited by the CETP inhibitor ([Sirtori, Mombelli, Clin. Chem, 2010](#)).

In regards to the rabbit studies: this started with the Okamoto paper in Nature ([2000](#)), which had one serious problem; the control group only had a final cholesterol of 129 mg/dl. Thus, in my view, the apparent advantage of giving JT-705 (dalcetrapib) makes no sense. A much better conducted study published by Huang ([Huang et al, Clin Sci, 2002](#)) used a similar protocol but had a

cholesterol of 757 mg/dl in the control group. In this study, in spite of a marked rise of HDL-C, there was no arterial benefit. This, in my view, should have closed the story. Unfortunately it did not.

The probucol data, on the other hand, are definitely of high significance. Probucol raises CETP and prevents arterial disease (a number of reports have recently come from Japanese investigators e.g. [Kasai *et al.* Atherosclerosis. 2012](#)). Most excitingly, it removes cholesterol deposits (xanthelasma/xanthomas) thus indicating that increased CETP is beneficial in man. Another negative issue to be raised is that in the Brusseau paper ([ref 40](#)) there was no evidence of a reduced cholesterol pool/increased fecal steroid excretion following torcetrapib, indicating again that blocking CETP does not in any way improve cholesterol turnover. I tend to believe that the issue of apo A-I synthesis is not of major significance. The reduction of AI synthesis (probucol) and increased synthesis (torcetrapib) is therefore of little interest.

In conclusion the author has certainly done a very good job but the paper would be improved by the inclusion of some older data, that in my view are more significant, vs data provided by the recent overviews or Mendelian randomizations.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 17 July 2014

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Gerald F. Watts

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This is an exceptionally good review and balanced assessment of the status of CETP inhibitors and ASCVD from a world authority in the field. The article highlights important data that might have been overlooked when promulgating the clinical value of CETPIs and related trials.

Only 2 areas need revision:

1. Page 3, para 2: the notion that these data from Papp *et al.* convey is critical and the message needs an explicit sentence or two at end of paragraph.
2. Page 4, Conclusion: the assertion concerning the ethics of the two Phase 3 clinical trials needs toning down. Perhaps rephrase to indicate that the value and sense of doing these trials is open to question, with attendant ethical implications, or softer wording to that

effect.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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