CETP inhibitors and cardiovascular disease: Time to think again
[v1; ref status: indexed, http://f1000r.es/3mp]

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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.
Background
Cholesteryl ester transfer protein (CETP) is a hydrophobic glycoprotein in plasma that catalyzes the transfer of neutral lipids between plasma lipoproteins. 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 Havel 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 preβ-HDLs that are the primary acceptors of cholesterol via the ABCA1 transporters in cell membranes. 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 transfer induced atherosclerosis in mice and that CETP inhibition prevented atherosclerosis in rabbits, drug discovery programmes made rapid progress.

The case for inhibition was weakened when later studies of CETP transgenic mice contradicted the earlier findings, and the incidence of CHD was not found to be significantly reduced in familial CETP deficiency. Studies of the relation of CHD to single nucleotide polymorphisms (SNPs) of the CETP gene yielded disparate outcomes, which were not resolved by meta-analyses. When Dullaart et al. meta-analyzed data on the TaqIB 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 2004. In June 2007, the trial was terminated after it had become clear that the treatment had increased the incidence of cardiovascular disease (CVD) events in healthy subjects; two of second events in subjects with an existing history of CHD; and in one study primary and secondary events were pooled. In two studies that looked at mortality in addition to CVD morbidity this was also negatively associated with CETP. Results in subjects taking pravastatin or atorvastatin mirrored those in other subjects. The suggestion in the earlier case-control study that subjects with raised triglycerides might differ from others was not confirmed.

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 CETP. 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 separately. Three were of first CVD events in healthy subjects; two were of second events in subjects with an existing history of CHD; and in one study primary and secondary events were pooled. In two studies that found the relation between CVD events and CETP concentration to be linear, one study did not appear until July 2006, two years after ILLUMINATE had started. Since then five further similar studies have been published.

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. 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 MI.

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. 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.

As discussed by several authors, genome-wide analyses are also not without their limitations, and several aspects of the two studies
III. CETP and Inverse HDL Cholesterol Risk

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 study 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 syndrome. 

**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. found that hepatic CETP gene transfer in mice stimulated the transport of cholesterol from peripheral macrophages to the liver, followed by its elimination as bile acids. Tchoua et al. 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. Villard et al. showed further that addition of purified CETP increased both the preβ-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 deficiency. 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. 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 atherosclerosis. By contrast, inhibition of CETP with torcetrapib had no effect on apo AI synthesis in humans. It is also worth noting that probucol, which increases CETP activity, also prevents atherosclerosis in rabbits despite lowering apo AI synthesis rate.

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 ILLUMINATE made no reference to the results of Marschang et al. published the year before. Likewise, the report on Dal-OUTCOMES 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 ILLUMINATE, and of several recent review articles.

**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. 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) 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 evacetrapib in preventing CVD events. REVEAL (NCT01252953), commenced in 2011 and expected to be completed in 2017, has enrolled 30,624 patients for a similar study of anacetrapib. 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) to lower LDL cholesterol by 50 per cent compared with the 25 per cent achieved with torcetrapib. 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 events.

**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 balance. 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.

**Grant information**

The author(s) declared that no grants were involved in supporting this work.


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Referee Responses for Version 1

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Approved: 29 July 2014

Referee Report: 29 July 2014
doi:10.5256/f1000research.4705.r5614

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 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 (xanthelasmas/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.

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

Competing Interests: No competing interests were disclosed.

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Approved: 17 July 2014

Referee Report: 17 July 2014
doi:10.5256/f1000research.4705.r5462
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.

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

Competing Interests: No competing interests were disclosed.