CETP, the human genome and cardiovascular outcomes

Epidemiological studies have provided evidence that elevated levels of high density lipoprotein cholesterol (HDL-C) and apo A-1 afford protection against cardiovascular disease [1, 2]. HDL-C levels, which are to a marked extent genetically determined, show in general an inverse relationship to coronary heart disease [3].

To understand causal pathways and assess the impact on cardiovascular risk, it is important to consider whether genetic polymorphism will influence an intermediate phenotype such as LDL-C or HDL-C. The study of Biedermann and colleagues considered the common single nucleotide polymorphisms (SNPs) with a high impact on individual cardiovascular risk, and showed that CETPrs708272 may help to predict cardiovascular outcome.

In the light of the evidence available, the most solidly established relationship is that between low density lipoprotein cholesterol (LDL-C)-related genes and coronary heart disease. Recent work has shown that individuals with polymorphism in PCSK9 have not only reduced levels of LDL-C but also a lower incidence of cardiovascular events [4]. This evidence is supported by other studies demonstrating that several other LDL-related pathways determine both plasma LDL-C levels and cardiovascular risk.

However, the evidence for genes that are known to influence HDL-C levels and the relationship to cardiovascular outcomes is much less clear, particularly where CETP is concerned.

Cholesterol ester transfer protein (CETP) mediates the transfer of cholesteryl esters between HDL particles and from HDL to other lipoproteins [5]. In this context it also plays a key role in the reverse transport of cholesterol from the periphery to the liver [6]. Individuals who are genetically CETP deficient or have genetic mutations of CETP often have extremely high HDL-C levels.

In view of the current discussion regarding CETP and the potential benefits from modifying CEPT activity, it is important to consider the available evidence in its entirety, in this case the genetic information specifically.

In a recent paper by Paul Ridker et al. [7] evidence was presented from a large cohort of more than 18 000 initially healthy female subjects of European ancestry from the Women’s Genome Health Study. In a genome-wide scan 350 000 SNPs at the CETP locus were found to be strongly associated with future risk of myocardial infarction, supporting a causal role for CETP in atherothrombosis, possibly through an HDL-C mediated pathway. Specific polymorphisms were found in or near the CETP gene which impact on future risk of myocardial infarction. Importantly, after adjustment for HDL-C levels at baseline the risk was attenuated but not completely abolished, suggesting that a factor beyond HDL-C elevation could be a key driver. It was further reported that the effects of the CETP SNPs on myocardial infarction risk were concordant with their effects on HDL-C. Hence, if a polymorphism was associated with increased levels of HDL-C the risk of myocardial infarction was reduced, and vice versa.

These results are consistent with another meta-analysis by Thompson et al. [8]. This literature review and meta-analysis of 92 studies published between January 1970 and January 2008 assessed the associations of CETP genotypes with CETP phenotypes, lipid levels and coronary risk. Three CETP genotypes were found to be associated with moderate inhibition of CETP activity and therefore modestly higher HDL-C levels. These genotypes showed weak inverse associations with coronary risk. Importantly, the odds ratios for coronary disease were consistent with the predicted reduction in cardiovascular risk for an equivalent increase in HDL-C.

In contrast to this is a 10-year follow-up of a cohort of male symptomatic coronary artery disease (CAD) by Riegeli et al. [9]. They describe a pharmacogenetic interaction between the CETP genotypes, statin therapy and clinical outcome. They reported that the CETP genotype TaqIB2 allele is associated with a lower level of CETP and a higher HDL-C, which adversely affected clinical outcome assessed by increased 10-year mortality in the presence of a co-prescribed statin. This study suggests that the reduction in cardiovascular events by statin therapy may depend on CETP genotype and associated CETP plasma levels. Importantly, however, follow-up data was not complete for all patients and the placebo group was only on statin for eight of the ten years. In addition, the study was conducted only in male patients and, after the initial two years, patient adherence to therapy was not known.

Further information is provided in a meta-analysis performed by Boekholt et al. [10] on individual patient data in 13 677 individuals from 7 large population-based studies and 3 randomised placebo-controlled pravastatin trials. They reported the relationship between TaqIB genotype,
HDL-C levels and coronary artery disease risk. After adjustments the TaqIB genotype exhibited a highly significant association with HDL-C and was significantly associated with the risk of coronary artery disease. Interestingly, after additional adjustment for HDL-C levels they found no statistical significance and no pharmacogenetic interaction between TaqIB genotype and pravastatin treatment. This study also reported that the significant association between TaqIB genotype and coronary artery disease risk was substantially attenuated on adjustment for HDL-C levels, suggesting that the association between TaqIB genotype and coronary artery disease risk is related to the plasma HDL-C level.

The influence of CETP gene mutations has also been reviewed in two papers from the Honolulu Heart Program [11, 12]. In each of these studies two different CETP gene mutations were evaluated in more that 3400 men of Japanese ancestry. These were associated with decreased CETP (−35%) and increased HDL-C levels (+10%). However, the overall prevalence of coronary heart disease was 21% in men with and 16% in men without mutations. This increased risk of an event also persisted after adjustments for cardiovascular risk factors and HDL. Interestingly, it was reported that high HDL-C and the Int 14A variant of the CETP gene may increase longevity. The conclusion drawn from these studies was that genetic CETP deficiency appeared to be an independent risk factor for cardiovascular outcomes. Although this study was conducted in a minority US population, the findings add further evidence that high HDL-C levels may protect against cardiovascular mortality. One final study meriting consideration is a prospective population-based study in 8141 chiefly Caucasians individuals [13]. During a median follow-up of 4.94 years the relationships between CETP polymorphisms, serum lipids, CRP and cardiovascular outcomes were evaluated. This study concluded that −629A as well as the TaqIBB2 and the I405VV alleles of the CETP gene were not associated with a lower coronary disease risk, despite the HDL-C boosting effect of these common CETP polymorphisms. As could be predicted from epidemiological evidence, the incidence of coronary disease was inversely related to baseline HDL-C levels. Nevertheless, the relationship of the −629A allele to increased risk of cardiovascular events was significant, and the risk associated with the B2 allele was greater after adjustment for the HDL-C level. The authors concluded that a common CETP promoter polymorphism, which contributes beneficially to higher HDL-C, is paradoxically associated with a higher incidence of coronary disease in the general population. Thus, CETP gene variation may affect coronary risk irrespective of the level of HDL-C.

From a review of this evidence the complexity of the CETP genetics is clear. Based on epidemiological and other evidence from clinical trials such as those with the statins, it has been hypothesised for some time that reducing CETP activity will raise HDL-C and therefore improve cardiovascular outcomes. However, the debate on the potential relationship of CETP, HDL-C and cardiovascular outcomes has intensified even further following the results of the torcetrapib clinical trials.

The development of torcetrapib, the first CETP inhibitor to go into large scale clinical trials, was halted due to significant adverse cardiovascular effects in the ILLUMINATE trial [14]. In addition, lack of benefit for atherosclerosis in IMT and IVUS studies was also reported [15–18]. Since these data were published there has been considerable debate as to whether CETP and/or HDL-C are in fact even causal for heart disease and even remain viable pharmacological targets.

One argument for continuing to target CETP as a mechanism for improving cardiovascular outcomes is that it is widely considered that torcetrapib, by an off-target mechanism unrelated to CETP inhibition, induces production of aldosterone and raises blood pressure. Several studies have now shown that it is not the CETP inhibition itself that causes the toxicity, but that the effect was rather compound-specific (torcetrapib) [19].

The effect of acting on CETP will only be truly determined by an outcomes study with a CETP inhibitor devoid of off-target effects such as those reported with torcetrapib. Such studies will also help to answer some of the remaining questions around HDL and “HDL functionality”. The functionality of the HDL particle has for some time been a topic of intense debate. Unlike LDL-C, where lower levels are clearly correlated with improved cardiovascular outcome, a high HDL-C level may not necessarily correlate with a reduction in cardiovascular events.

Currently two CETP inhibitors, dalcetrapib and anacetrapib, are in late-stage development. These molecules appear to bind differently on CETP, to reduce CETP activity and thus result in different magnitudes of effect on the HDL-C and LDL-C levels. The true meaning of these differences will become apparent after completion of outcome trials. The dal-OUTCOMES study [21] with dalcetrapib is currently ongoing and trials with other CETP inhibitors are in the planning phase. In a trial of this kind it will be possible to perform analyses to elucidate relationships between cardiovascular outcomes and changes in plasma HDL-C concentrations, as well as CETP mass and activity in statin-treated patients. It will also be possible to investigate the relationship of CETP polymorphisms, such as that assessed in the paper by Biedermann and colleagues, to cardiovascular outcome.

Until the first of these studies is completed the debate surrounding CETP and the impact of CETP inhibitors on cardiovascular outcomes remains at equipoise.

The study by Biedermann and colleagues adds further information to the discussion of the genet-
ics of CETP and the relationship of CETP, HDL-C and cardiovascular outcome. It also suggests that CETP polymorphisms may in future be used to identify patients at risk of cardiovascular events. This could eventually be translated into selection of specific therapeutic approaches to improve cardiovascular outcomes as part of a personalised healthcare programme.

References


5 Barter, et al. HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular outcomes as part of a personalised healthcare programme.


