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Link to published version (if available):
10.1038/nrcardio.2017.156

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REVEALing the effect of CETP inhibition in cardiovascular disease

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Introduction

For decades, the scientific community has been perplexed about the incongruent relationship of blood cholesterol concentrations and risk of coronary heart disease (CHD). This is borne out of the strong observational relationships of both low- (LDL-C) and high- (HDL-C) density lipoprotein cholesterol with risk of CHD. While a causal role for LDL-C is well-established from multiple randomized trials of drugs that alter LDL-C, the role of HDL-C remains much less clear. The enzyme cholesterol ester transfer protein (CETP) exchanges cholesterol from HDL particles to very low density lipoprotein particles in exchange for triglycerides and treatment with potent CETP inhibitors leads to an elevation of HDL-C and a reduction in Friedewald-measured LDL-C. Initial phase III randomized controlled trials (RCTs) of CETP inhibitors failed due to lack of efficacy and/or adverse effects, but the REVEAL trial recently reported a beneficial effect for CHD.[1] In this Comment, we summarise the evidence for CETP inhibitors in the context of genetic studies.

HDL-C as a predictor of CVD

Traditional observational studies provide strong evidence that HDL-C is independently inversely associated with future risk of CHD and stroke in prospective cohorts. The association of HDL-C with risk of CHD remains present even when adjusting for triglycerides and other potential confounders. However, whereas the path to showing LDL-C to be causal in CHD has been smooth with orthogonally-targeted pharmaceutical agents (statins, ezetimibe and PCSK9 inhibitors) providing consistent evidence from RCTs, the path has been

much more tortuous for drugs principally targeting HDL-C. The robust association of HDL-C with CHD in observational data does provide clinical utility for disease prediction; indeed HDL-C is included in many risk prediction scores. However, utility for disease prediction is quite distinct to causality. Despite the prevailing view being that the evidence for causality of HDL-C was very strong (as evidenced by the huge investment in RCTs) over quarter of a century ago it was demonstrated that the statistical robustness of the epidemiological evidence was suspect[2]. More recently, studies have sought to clarify the role that HDL-C has in cardiovascular diseases (CVD) using both genetic and interventional study designs.

Genetic evidence of HDL-C

The most notable Mendelian randomization (MR) study of HDL-C by Voight and colleagues in 2012 did not provide evidence of causation (as summarised in a recent MR review[3]). From a modern MR perspective, the approach by Voight et al could be considered limited as the instrument consisted of only 14 single nucleotide polymorphisms (SNPs) that had been manually pruned to remove SNPs that also showed associations with LDL-C and TG: in the two-sample MR design, this could lead to a false negative association in the presence of weak instrument bias, and the selection of the SNPs in such a way may not be objective and could introduce bias[3]. However, subsequent studies using many larger sets of SNPs identified from GWAS of HDL-C and more contemporary MR approaches (that take into account genetic pleiotropy) have also shown a neural association of HDL-C with CHD risk.[4] This has led to the prevailing interpretation that circulating levels of HDL-C are unlikely to play an important role in the aetiology of CHD.

Genetic evidence of CETP

MR of a biomarker (such a HDL-C) is quite distinct to MR of a drug target, as drug targets tend not to show specificity for the exposure of interest. Early studies provided weak evidence that *CETP* genetic variants were linked to CHD risk, however more recent large-scale evidence provides robust associations, including the identification of a variant in *CETP* associated with CHD at $P = 9.8 \times 10^{-9}$ in a recent hypothesis-free GWAS.[5] Furthermore, a very recent factorial MR study[6] provided new insights that predicted the clinical effect of CETP inhibition, when given with a statin, might be exaggerated if LDL-C is used as a marker of CETP drug efficacy as opposed to apolipoprotein B, as reported in REVEAL.[1]

Treatment trials of CETP inhibitors

The first phase III trial of a CETP inhibitor (ILLUMINATE[7]) randomized 15,067 patients at high cardiovascular risk to torcetrapib or placebo. Torcetrapib raised HDL-C by 72% and lowered LDL-C by 25% but the trial was terminated due to 25% higher risk of major vascular events in those randomized to torcetrapib, linked to elevated systolic blood pressure (SBP). Of note, higher SBP associations were also identified for all other CETP inhibitors tested in phase III RCTs (including dalcetrapib, evacetrapib and anacetrapib). dal-OUTCOMES[8] randomized 15,871 patients with a recent acute coronary syndrome to dalcetrapib or placebo.

Dalcetrapib increased HDL-C by 31-40% but had minimal effect on LDL-C and dal-OUTCOMES was terminated due to futility, with the hazard ratio (HR) for the primary endpoint of major vascular events being 1.04 (0.93,1.16) for dalcetrapib vs placebo. In the subsequent ACCELERATE trial[9], 12,092 with established vascular disease were randomized to receive evacetrapib or placebo. Evacetrapib, an efficacious CETP inhibitor, increased HDL-C by 132% and lowered LDL-C by 37%, but ACCELERATE was also terminated after an average 25 months of treatment owing to futility, with the HR of the primary endpoint of major vascular event for evacetrapib vs placebo being 1.01 (95%CI: 0.91, 1.11). Most recently, and as a surprise to the cardiovascular community, the REVEAL[1] trial of anacetrapib, another potent CETP inhibitor, reported a beneficial effect. In REVEAL, 30,449 patients with prior vascular disease were randomized to anacetrapib or placebo. Anacetrapib treatment led to a 104% increase in HDL-C and a 17 or 41% reduction in LDL-C (for LDL-C measured by beta-quantification and direct method, respectively) and yielded a HR of 0.91 (0.85 to 0.97) of major coronary events, compared to placebo.[1]

Putting the evidence together

How do we explain the incongruent findings between multiple trials of CETP inhibitors, *CETP* genetics and HDL-C? First, the findings from REVEAL[1] do not change the prevailing notion that circulating levels of HDL-C are unlikely to play an important role in the aetiology of CHD. To expand, CETP inhibitors that had no large effect on atherogenic lipoproteins (LDL-C or apolipoprotein B) had no association with CHD. Second, the magnitudes of effect for both non-HDL-C and corresponding risks of CHD reported in REVEAL are entirely consistent with those from treatment trials of statins, ezetimibe and PCSK9 inhibitors (**Figure**), and the genetic associations that correspond to these drug targets line up on a steeper slope which is expected given that the effect of atherogenic lipoproteins on cardiovascular risk is accumulated over a lifetime. Third, the neutral finding in ACCELERATE of evacetrapib, a drug that did have strong effects on non-HDL-C, is likely to have arisen from premature termination of the trial, as exemplified by the stratification of findings from REVEAL by years of follow-up: at 2 years, the estimate for major coronary events from REVEAL was RR 0.96 (0.84–1.10) which overlaps the major vascular estimates from ACCELERATE (1.01; 0.91 to 1.12). Furthermore, in REVEAL, the estimate for major coronary events was stronger than major vascular events, meaning that ACCELERATE may also have been hindered by use of a primary endpoint comprising a composite that included elements that may have attenuated the association.

Moving forward, key questions include: (i) the mechanism of increase in SBP that is seen in treatment with CETP inhibitors, which, with the exception of torcetrapib (where there was very likely an excess SBP effect), the modest SBP signal appears to be in ratio to the degree of HDL-C raising and could therefore be target-mediated; (ii) whether therapeutic inhibition of CETP leads to age-related macular degeneration, as predicted by genetic studies[10], but for which REVEAL was underpowered to detect; (iii) whether CETP inhibitors alter risk of diabetes (a modest beneficial effect was seen in both REVEAL and ACCELERATE); (iv) which

patients might derive clinical benefit from CETP inhibitors; and, (v) the cost-effectively of such treatment. Certainly, the findings from REVEAL brings to a close the long-standing worrisome discordance between multiple MR findings (that anticipated cardiovascular benefit from therapeutic inhibition of CETP) and multiple phase III clinical trials (that, prior to REVEAL, showed no such benefit). For lipidoligists, the accumulating data point towards a unifying theory of apolipoprotein B driving CHD, and it may be back to the drawing board for HDL.

Conflicts of interest

The authors do not report any disclosures.

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Figure Legends

Figure. Treatment trials of drugs and natural trials of genes that modify non-HDL-C and risk of coronary heart disease.

Treatment trials are represented by circles and solid vertical lines, whereas genetic proxies are represented by squares and dashed vertical lines. The three cholesterol treatment trialists' (CTT) collaboration values (plotted in mint green) from left to right are: (i) 5 more-vs-less statin trials; (ii) 17 statin-vs-placebo trials with non-HDL differences <50 mg/dL; and, (iii) 4 statin-vs-placebo trials with non-HDL differences >50mg/dL and, together with the data from REVEAL, are derived from Figure S5 of the REVEAL trial publication[1] with estimates obtained using 'PlotDigitizer' (http://plotdigitizer.sourceforge.net/). Values for the genetic variants are taken from Figure 2C in Ference et al,[6] scaled to the same difference in non-HDL-C as the corresponding treatment trials, using apolipoprotein B as a proxy for non-HDL-C. CHD end-points in trials comprise: REVEAL and CCT: coronary death or MI; IMPROVE-IT and FOURIER: MI. End-point in Ference et al[6] is MI, coronary revascularization, stroke or coronary death.