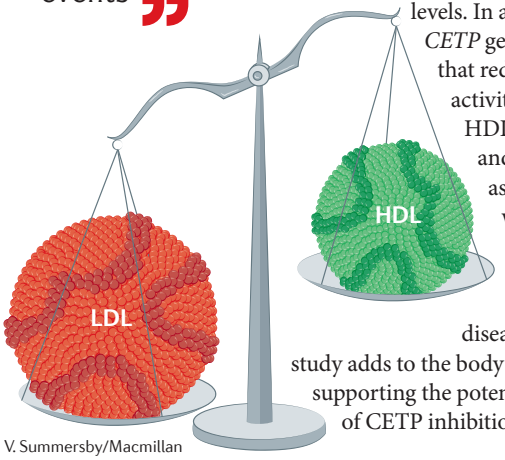
Nature Reviews Cardiology | Published online 1 Jun 2017; doi:10.1038/nrcardio.2017.87

DYSLIPIDAEMIA

Is CETP inhibition a viable therapeutic strategy?

> CETP inhibition does not reduce the rate of cardiovascular events

The rationale for targeting cholesteryl ester transfer protein (CETP), an enzyme that promotes the transfer of cholesteryl esters from HDL to very low-density lipoprotein and LDL, to reduce the risk of cardiovascular disease is that CETP inhibition raises HDL-cholesterol (HDL-C) levels and decreases LDL-cholesterol (LDL-C) levels. In addition, *CETP* gene variants that reduce CETP activity increase HDL-C levels and have been associated with a lower risk of cardiovascular disease. A new study adds to the body of evidence supporting the potential efficacy of CETP inhibition.



V. Summersby/Macmillan Publishers Limited

Kathiresan and colleagues sequenced the *CETP* exons in 18,817 patients with coronary heart disease (CHD) and 39,652 participants without CHD and found that carriers of a protein-truncating variant in *CETP* (about 1 in 975 participants) had higher levels of HDL-C and lower levels of LDL-C and triglycerides than noncarriers. Moreover, mutation carriers had a lower risk of CHD.

Despite these promising results, so far none of the CETP inhibitors assessed in clinical trials has shown benefits in improving cardiovascular outcomes. The latest trial on a CETP inhibitor, the ACCELERATE trial on evacetrapib, confirms these neutral findings. This trial, which included 12,092 patients with high-risk vascular disease, showed that CETP inhibition does not reduce the rate of cardiovascular events compared with placebo when added to standard therapy, despite inducing a 133.2% increase in HDL-C levels (1.6% increase with placebo) and a 31.1% reduction in LDL-C levels (6.0% increase with placebo). The trial was terminated early because of futility.

Several explanations have been proposed for the lack of beneficial effect of CETP inhibitors on cardiovascular outcomes, including off-target adverse effects, the type of patients included in the trials, or concurrent use of statins. Most importantly, carriers of a *CETP* gene variant have had a lifelong perturbation of CETP, whereas pharmacological CETP inhibition is initiated later in life. Results from a phase III trial on another CETP inhibitor, anacetrapib, are expected this year.

Irene Fernández-Ruiz

ORIGINAL ARTICLES Nomura, A. *et al.* Protein truncating variants at the cholesteryl ester transfer protein gene and risk for coronary heart disease. *Circ. Res.* http://dx.doi.org/10.1161/CIRCRESAHA.117.311145 (2017) | Lincoff, A. M. *et al.* Evacetrapib and cardiovascular outcomes in high-risk vascular disease. *N. Engl. J. Med.* **376**, 1933–1942 (2017)
FURTHER READING Rosenson, R. S. *et al.* Dysfunctional HDL and atherosclerotic cardiovascular disease. *Nat. Rev. Cardiol.* **13**, 48–60 (2016)