EDITORIAL

The future of CETP inhibition – still to be REVEALed

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Key words

CETP inhibitors, dyslipidaemia, HDL cholesterol

doi: 10.5837/bjc.2012.022

Br J Cardiol 2012;**19**:104–06

In this issue (see pages 126–33), Paul Durrington has written an excellent review of one of the most interesting conundrums in current clinical lipidology – the putative role of cholesteryl ester transfer protein (CETP) inhibitors.

Reducing the residual cardiovascular risk that remains after statin use is a frontline challenge for preventive cardiology. After attention to other modifiable risk factors, further reduction of low-density lipoprotein cholesterol (LDL-C) levels and increasing high-density lipoprotein cholesterol (HDL-C) levels are under particular scrutiny.[1,2] The cardioprotective epidemiology of HDL-C is strong and well known, and so it often comes as a shock to health professionals that there is no direct proof that raising HDL-C improves cardiovascular outcomes. Despite this, raising HDL-C remains an attractive potential approach for tackling residual risk as many patients already achieve very low LDL-C levels on treatment and even at these low levels, HDL-C still predicts cardiovascular outcomes.[3]

Levels of complexity

High-density lipoproteins are complex lipoproteins about which much remains to be understood. Their diverse protein content and multiple structures and functions suggest a number of potential mechanisms by which they may offer protection against cardiovascular disease. What has become clear though, is that simple measurement of the level of HDL-C is not a determinant of its functional capacity and the pressure is on to find a measure that is.[4]

CETP inhibitors raise HDL-C levels by inhibiting the transfer of cholesterol ester from HDL to larger lipoproteins such as chylomicrons, very-low-density lipoprotein (VLDL) and LDL. The experience of the first in class, torcetrapib, is well known, as the ILLUMINATE study was terminated early due to an excess of deaths in the treatment group.[5] Subsequent investigations suggested that torcetrapib has an off-target hypertensive effect but this in itself may not be enough to explain all the deaths. As a result, the development of additional CETP inhibitors has been cautious but neither dalcetrapib, anacetrapib nor evacetrapib have, as yet, shown apparent off-target side effects.

Trial failure

On 7th May, a trial (Dal-OUTCOMES) investigating the safety and efficacy of dalcetrapib in stable coronary heart disease (CHD) patients on a statin was terminated a year early by its data and safety monitoring board as no clinical benefit was becoming apparent. As a result, the development programme of dalcetrapib has been halted. Compared with anacetrapib and evacetrapib, dalcetrapib is a weaker CETP inhibitor with smaller effects on HDL-C and almost no effect on LDL-C. Its advantage was thought to lie in the fact that its inhibition fell short of attenuating CETP-mediated HDL remodelling, thereby encouraging the formation of pre-β HDL thought to be important as a cholesterol acceptor from peripheral tissues.[6] For some, the trial cessation was not unexpected as surrogate trials on brachial artery reactivity (as an index of endothelial function) and plaque imaging had been, respectively, negative and neutral.[7,8]

There are theoretical reasons why CETP inhibitors may not deliver their promise and this underlines the need for properly conducted clinical outcome trials. As Professor Durrington explains, CETP contributes to reverse cholesterol transport, as some of the cholesterol accepted from HDL is taken up by the liver by LDL or chylomicron remnant receptors. Interfering with this may be pro-atherogenic, especially if conventional reverse cholesterol transport via the scavenger receptor class B1 (SR-B1) receptor in the liver is saturated. It is also possible that the enlarged HDL particles derived through CETP inhibition may be dysfunctional, although *in vitro* experiments with HDL derived from torcetrapib in the ILLUMINATE trial did show increased cellular cholesterol efflux.[9] In addition, adverse effects on nitric oxide stimulation, endothelin-1 secretion, apolipoprotein A-1 modification and innate immunity have all been proposed.

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Continued development

At present, both anacetrapib and evacetrapib are continuing their development. These high-intensity CETP inhibitors can both deliver HDL-C elevations in excess of 130% and LDL-C reductions of around 40%. Remarkably, these changes still occur despite background statin use. The HPS3 TIMI 55 REVEAL trial, run by Oxford University, is investigating the effects of anacetrapib in addition to atorvastatin in over 30,000 people with atherosclerotic vascular disease over a four-year period. Given the large reduction in LDL-C induced by additional anacetrapib, it is hard to imagine this trial will not be positive when it reports in 2017. The contribution of the increased level of HDL-C, however, may still be difficult to quantify.

Winston Churchill once described Russia as "a riddle wrapped in a mystery inside an enigma". The same can be said of CETP inhibition, the difference being that proper clinical investigation will unlock the puzzle and potentially herald a major new era in residual risk reduction

Conflict of interest

None declared.

Editors' note

See also the article by Professor Paul Durrington on pages 126–33 of this issue.

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