Reduction in PCSK9 levels induced by anacetrapib: an off-target effect?¹

Philip J. Barter,² Fatiha Tabet, and Kerry-Anne Rye, Associate Editor

School of Medical Sciences, University of New South Wales Australia, Sydney, Australia

Inhibitors of proprotein convertase subtilisin/kexin type 9 (PCSK9) and cholesteryl ester transfer protein (CETP) are both under current investigation as agents with the potential to reduce atherosclerotic cardiovascular disease (ASCVD) risk. Inhibitors of PCSK9 reduce the concentration of LDL cholesterol by more than 60%, while inhibitors of CETP reduce LDL cholesterol by up to 45% and increase HDL cholesterol by up to 180%.

The existence of PCSK9 was first reported in 2003 (1). Since that time, there has been extensive investigation of this enzyme, culminating in the development of PCSK9 inhibitors that are now approved therapeutics in the United States and which are undergoing long-term cardiovascular outcome trials. PCSK9 is expressed mainly in the liver (2), from which it is secreted into plasma. Activity of PCSK9 reduces the number of LDL receptors on the surface of cells and therefore impacts adversely on the removal of LDL from plasma (1, 3).

In the absence of PCSK9, LDLs bind to LDL receptors on the cell surface to form LDL/LDL receptor complexes that are taken up into the cell. The lower pH inside the cell promotes dissociation of the LDL receptor from the complex, leaving it to recycle back to the cell surface (4). The released LDL particle enters lysosomes, where it is degraded. When PCSK9 is present in plasma, it binds to LDL receptors on the cell surface (1). The subsequent binding of an LDL to the receptor results in the formation of a complex consisting of an LDL receptor, an LDL, and a molecule of PCSK9. When this complex enters the cell, the presence of PCSK9 prevents dissociation of the LDL receptor from the complex (5). Rather, the whole complex, including the LDL receptor, is transported to lysosomes for degradation. As a consequence, the LDL receptor is no longer able to recycle back to the cell surface. The end result of activity of PCSK9 is, therefore, a reduction in the number of LDL receptors on the cell surface. Inhibitors of PCSK9 increase cell surface LDL receptor expression and reduce LDL cholesterol levels by more than 60% (6).

Gain-of-function mutations of PCSK9 decrease the number of LDL receptors on the cell surface and represent a rare cause of familial hypercholesterolemia (7), while loss-of-function mutations of PCSK9 result in an increased number of LDL receptors on the cell surface, which leads to a lifelong low level of LDL cholesterol (8) and a markedly reduced ASCVD risk (9, 10).

CETP is also synthesized mainly in the liver and is secreted into plasma where it promotes bidirectional transfers and, thus, equilibration of both cholesteryl esters and triglyceride between plasma lipoprotein particles (11). Because most of the cholesteryl esters in plasma originate in the HDL fraction, this equilibration results in a net mass transfer of cholesteryl esters from HDL to the VLDL and LDL fractions. Inhibition of CETP blocks these transfers, decreasing the concentration of LDL cholesterol by up to 45% and increasing the concentration of HDL cholesterol by up to 180% (12–15).

Despite these effects on plasma lipid levels, and despite compelling genetic evidence supporting the potential of CETP inhibition as an anti-atherogenic strategy (16), two large clinical outcome trials with the CETP inhibitors torcetrapib and dalcetrapib failed to demonstrate any reduction in ASCVD events (12, 17). Understandably, these failures have generated considerable uncertainty about the value of CETP inhibition. It should be noted, however, that the failure of torcetrapib may have been the consequence of serious adverse off-target effects of a flawed drug (12) and that the failure of dalcetrapib may have reflected an inability of the drug to lower the level of LDL cholesterol (17). It is therefore premature to abandon the hypothesis that CETP inhibition is anti-atherogenic. Indeed, the hypothesis is currently being tested in two large clinical outcome trials using the CETP inhibitors anacetrapib (ClinicalTrials.gov number: NCT01252953) and evacetrapib (ClinicalTrials.gov number: NCT01687998). These trials should provide an answer in the reasonably near future as to whether inhibition of CETP does or does not reduce ASCVD events.

The mechanism by which CETP inhibition impacts on LDL is unclear. While a reduction in the concentration of cholesterol in LDL can be explained in terms of a block in the transfer of cholesteryl esters from HDL to LDL, this cannot explain the observed reduction in the concentration

²To whom correspondence should be addressed. e-mail: p.barter@unsw.edu.au
of LDL particles, as reflected by a decrease in plasma levels of apoB. Treatment with the CETP inhibitors, torcetrapib, anacetrapib, evacetrapib, and TA-8995, reduces the plasma concentration of apoB (12–15). In the case of both torcetrapib (18) and anacetrapib (19), this is the consequence of an enhanced clearance from plasma of the apoB contained in both the VLDL and LDL fractions, and most likely reflects an increase in the number of cell surface LDL receptors.

The ability of CETP inhibitors to increase the number of LDL receptors on the cell surface may be secondary to the reported ability of CETP inhibition to enhance the HDL-mediated efflux of cholesterol from cells (14, 20, 21). The resulting reduction in cell cholesterol concentration would be predicted to activate sterol regulatory element-binding protein-2 (SREBP-2) that, in turn, would increase the synthesis of LDL receptors (22). However, activation of SREBP-2 is also known to increase the synthesis of PCSK9 (23). It was therefore quite unexpected to find that treatment with anacetrapib (given as monotherapy) decreased rather than increased plasma levels of PCSK9 in rhesus macaques (24) and humans (19). However, given to humans who were also taking atorvastatin, anacetrapib reduced the concentration of LDL apoB, but had no effect on the level of PCSK9 (19). The explanation for any anacetrapib-induced reduction in PCSK9 is unclear because, whether given as monotherapy or as add-on therapy in people treated with atorvastatin, anacetrapib had no effect on either the production rate or the fractional catabolic rate of PCSK9 (19). Clearly, the effect of CETP inhibition on PCSK9 in humans requires further investigation.

The ability of anacetrapib to reduce plasma levels of PCSK9 has now been confirmed in a study of CETP-expressing APOE*3-Leiden mice published in this issue of the Journal of Lipid Research (25). In this study, the investigators found that administration of anacetrapib decreased hepatic expression and plasma levels of PCSK9 and increased hepatic LDL receptor levels not only in animals expressing CETP, but also in APOE*3-Leiden mice that do not express CETP. This indicates that anacetrapib reduces PCSK9 levels in mice by an as yet unknown mechanism that is unrelated to the inhibition of CETP.

At present, it is not known whether the ability of anacetrapib to reduce plasma levels of PCSK9 is shared by other CETP inhibitors. It is also not clear how treatment with anacetrapib (or other CETP inhibitors) impacts on plasma levels of PCSK9 in humans and, if it does, whether the effect is CETP-dependent or -independent. Measurement of plasma levels of PCSK9 in humans treated with anacetrapib, evacetrapib, and TA-8995 is awaited with great interest.

REFERENCES


