Anacetrapib-driven triglyceride lowering explained: the fortuitous role of CETP in the intravascular catabolism of triglyceride-rich lipoproteins

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Atherosclerosis and associated CVD remains the largest cause of mortality worldwide (1). Despite substantial benefit offered by statin monotherapy, cardiovascular events still claim more lives than any other cause. To address this unmet therapeutic need, drug discovery efforts have shifted toward novel approaches to alter cholesterol metabolism that do not rely on inhibition of cholesterol synthesis. Elevation of HDL cholesterol has been a popular therapeutic strategy (2). However, recent clinical trials (3,4) have failed to show clinical benefits of HDL cholesterol elevation, and Mendelian randomization studies question the causal link between HDL cholesterol levels and CVD (5). These recent findings have called into question the importance of HDL cholesterol as a surrogate marker of protection from atherosclerosis (2). Despite the persistent debate surrounding the “HDL hypothesis”, there have been relentless efforts by major pharmaceutical companies to develop HDL cholesterol elevating therapies. Out of these efforts has come highly potent and selective inhibitors of cholesteryl ester transfer protein (CETP), which promote large increases in HDL cholesterol levels. The two decade-long story of CETP inhibitor development is reaching its final chapter, with what is likely the last hard endpoint trial concluding in 2017 (6, 7). What remains to be determined is whether the last standing CETP inhibitor developed by Merck Pharmaceuticals, known as anacetrapib, will provide benefit against coronary events.

Nearly four decades ago, the CETP story began with the seminal discovery that core lipids [cholesteryl esters and triglycerides (TGs)] of major lipoprotein particles can be enzymatically exchanged in the circulation (8, 9). Subsequent studies have demonstrated that CETP is responsible for the transfer of cholesteryl esters from HDL to apolipoprotein B-containing lipoproteins such as VLDL and LDL, while at the same time reciprocally transferring TGs from VLDL and LDL to HDL (10). Since the discovery and biochemical characterization of CETP, human genetic (11–13) and animal studies (14–16) have provided strong rationale for advancing CETP as a drug target. In the early 2000s, CETP inhibitors were envisioned as game changers in CVD drug discovery, yet the recent failures of three separate CETP inhibitors in randomized outcomes trials have caused concern that CETP may not be an ideal target (6, 7). However, it is important to note the failure of some of these trials stems from either off-target adverse effects, poor efficacy of CETP inhibition, or issues with trial design (6, 7). Despite these obvious hurdles, one of the most potent and selective CETP inhibitors, anacetrapib, has thus far withstood the negative results of other agents in this class, and we will soon know whether targeted CETP inhibition with anacetrapib provides therapeutic benefit. With final results expected in 2017, the Randomized Evaluation of the Effects of Anacetrapib Through Lipid-modification (REVEAL) trial (ClinicalTrials.gov # NCT01252953) is investigating the added benefit of anacetrapib to standard-of-care atorvastatin in more than 30,000 people with established atherosclerotic CVD.

Anacetrapib is remarkably effective in raising HDL cholesterol levels (138% increase), and also lowers LDL cholesterol by 40% (17). In addition to these expected effects of CETP inhibition, anacetrapib also lowers plasma TG levels (7%) and reduces levels of proatherogenic particle known as lipoprotein (a) [Lp(a)] by 36% (17). These significant effects on dyslipidemia are expected to protect against atherosclerosis, yet there has been continued debate on whether the large HDLs formed with CETP inhibition are “functional” (18, 19). Furthermore, there have been concerns raised about the predicted plasma TG-raising effects of CETP inhibitors (18, 19). Although not predicted by in vitro biochemistry studies, CETP inhibitors including anacetrapib modestly lower plasma TG levels (6, 7, 17). However, the mechanism underlying this TG lowering response has been elusive. In this issue of the Journal of Lipid Research, Millar et al. (20) provide important new insights into how anacetrapib treatment reduces circulating TG levels. Mechanisms underlying the TG-lowering associated with CETP inhibition were addressed by performing well-controlled stable isotope lipoprotein kinetic studies in subjects treated with anacetrapib monotherapy or anacetrapib plus atorvastatin (20). Interestingly, anacetrapib-mediated CETP inhibition increased the fractional catabolic rate.

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(FCR) of VLDL-TG when given either as a monotherapy or in conjunction with atorvastatin (20). In parallel with enhanced FCR, anacetrapib treatment also resulted in the redistribution of several key exchangeable apolipoproteins including apoC-II, apoC-III, and apoE on circulating lipoproteins (20). In subjects treated with anacetrapib plus atorvastatin the pool sizes for apoC-II, apoC-III, and apoE were all elevated (20), which would be expected to alter lipoprotein lipase activity as well as the clearance of remnant lipoproteins (21). However, identical effects on apolipoprotein distribution were not apparent with anacetrapib monotherapy, indicating potential drug-drug interactions that may impact intravascular lipoprotein metabolism (20).

The work by Millar et al. is an important contribution given it is one of the first studies to carefully monitor anacetrapib-driven alterations in VLDL-TG metabolism in humans. To date, almost all studies examining CETP’s role in VLDL-TG metabolism have been conducted in animal models including CETP-transgenic mice, hamsters, and non-human primates, all of which have dramatically different lipoprotein lipase activity and intravascular metabolism of TG-rich lipoproteins (14–16, 22–23). It is quite clear that anacetrapib is effective at altering atherogenic dyslipidemia [increased HDL cholesterol, decreased LDL cholesterol, decreased VLDL-TG, and decreased Lp(a)], but the jury is still deliberating on whether this will translate into a true benefit for those suffering from CVD. As the REVEAL trial results are scheduled to be unveiled some time later this year, the ultimate fate of the last standing potent CETP inhibitor, anacetrapib, will be determined. If anacetrapib is shown to reduce CVD events, follow-up studies will be needed to decipher whether the benefit resulted from increases in HDL cholesterol levels or, alternatively, reductions in LDL cholesterol, Lp(a), or triglyceride-rich lipoprotein levels. Given that Mendelian randomization studies suggest that circulating LDL cholesterol, VLDL-TG, and Lp(a) are causally linked to CVD (5, 24), it is tempting to speculate that anacetrapib will provide therapeutic benefit based solely on the its ability to reduce levels of these proatherogenic apoB-containing lipoproteins. The work by Millar et al. in this issue of the Journal of Lipid Research will serve as an important guidepost for subsequent mechanism of action studies if the CETP story does finally survive the test of time.

REFERENCES


