

Trials and Tribulations of CETP Inhibitors

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Abstract: The development of CETP (cholesteryl ester transfer protein) inhibitors has had a long and difficult course with 3 compounds failing in phase III clinical trials. Finally, the REVEAL (Randomized Evaluation of the Effects of Anacetrapib through Lipid modification) trial has shown that the CETP inhibitor anacetrapib decreased coronary heart disease when added to statin therapy. Although the result is different to earlier studies, this is likely related to the size and duration of the trial. The benefit of anacetrapib seems to be largely explained by lowering of non-HDL-C (high-density lipoprotein cholesterol), rather than increases in HDL-C. Although the magnitude of benefit for coronary heart disease appeared to be moderate, in part this may have reflected aspects of the trial design. Anacetrapib treatment was associated with a small increase in blood pressure, but was devoid of major side effects and was also associated with a small reduction in diabetes mellitus. Treatment with CETP inhibitors, either alone or in combination with statins, could provide another option for patients with coronary disease who require further reduction in LDL (low-density lipoprotein) and non-HDL-C. (*Circ Res.* 2018;122:106-112. DOI: 10.1161/CIRCRESAHA.117.311978.)

Key Words: anacetrapib ■ coronary disease ■ dalcetrapib ■ evacetrapib ■ torcetrapib

The development of CETP (cholesteryl ester transfer protein) inhibitors was motivated by the discovery that humans with genetic CETP deficiency have markedly elevated levels of HDL-C (high-density lipoprotein cholesterol), as well as reduced levels of LDL-C (low-density lipoprotein cholesterol), a profile that is typically associated with reduced atherosclerosis.¹ CETP inhibitors were subsequently shown to raise HDL-C levels, in some cases impressively; in addition the more potent CETP inhibitors lowered LDL-C levels. Based on epidemiological observations, it was expected that this marked increase in HDL would deliver a powerful antiatherogenic effect. This promise has not been realized in cardiovascular clinical outcome trials of CETP inhibitors. In fact, in the first large trial the CETP inhibitor torcetrapib caused an excess of deaths and cardiovascular disease (Table),² leading many to conclude that the elevated HDL itself was harmful. The identification of off target toxic side effects of torcetrapib² led to sufficient clinical equipoise to allow further evaluation of this class of drugs. Subsequent trials with the relatively ineffective CETP inhibitor dalcetrapib³ and with the potent inhibitor evacetrapib⁴ were stopped early for futility (lack of efficacy in reducing cardiovascular [CV] events). Now results from the largest and longest running trial of a CETP inhibitor, in this case the potent inhibitor anacetrapib, have been published, showing that this drug significantly reduced major coronary events.⁵ Although the magnitude of risk reduction was moderate, anacetrapib could find a place in the armamentarium of approved nonstatin lipid-targeted agents. However, this result leaves many questions unanswered, a few of which include (1) Why did this trial show benefit when other trials with CETP inhibitors did not? and (2) Given the reductions in LDL and non-HDL-C seen

with anacetrapib, did the increase in HDL-C contribute to the benefit? This review will attempt to address these questions, while providing a background on the role of CETP in lipoprotein metabolism, emphasizing genetic, and human metabolic studies. The reader is referred to earlier reviews for additional background on CETP.⁶⁻⁹

Reduction in Coronary Heart Disease With CETP Inhibition Is Revealed

The REVEAL (Randomized Evaluation of the Effects of Anacetrapib through Lipid modification) study involved 30 449 patients with atherosclerotic cardiovascular disease who were randomized to receive anacetrapib 100 mg daily or placebo on top of effective statin therapy and followed for a median of 4.1 years. After the failure of CETP inhibitors in 3 successive clinical trials, expectations were low that anacetrapib, a CETP inhibitor developed by Merck, would meet with success. However, REVEAL demonstrated a highly significant reduction (rate ratio, 0.91; $P < 0.004$) in the composite primary end point of coronary death, myocardial infarction (MI), or coronary revascularization.⁵ The individual components of the primary end point showed similar rate ratios but were only significant for MI and revascularization. The incidence of the prespecified outcome of coronary death or MI was significantly lower in the anacetrapib group (rate ratio, 0.89; $P = 0.008$). The secondary end point of major coronary event (MI, coronary death, or ischemic stroke) just missed significance (rate ratio, 0.93; $P = 0.052$). There was also a significant difference for the secondary outcome of major vascular events favoring anacetrapib. At the trial midpoint, anacetrapib raised HDL-C from 42 to 86 mg/dL (104%) and apoA-I (apolipoprotein) by 36%; in addition, it lowered LDL-C from 63 mg/dL to 53 mg/dL (−17%, as determined by

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Nonstandard Abbreviations and Acronyms

ACCELERATE	Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition with Evacetrapib in Patients with a High Risk for Vascular Outcomes
Apo	apolipoprotein
CETP	cholesteryl ester transfer protein
DEFINE	Determining the Efficacy and tolerability of CETP inhibition with anacetrapib
FOURIER	Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk
HDL-C	high-density lipoprotein cholesterol
IMPROVE-IT	The Improved Reduction of Outcomes: Vytorin Efficacy International Trial
LDL-C	low-density lipoprotein cholesterol
LP(a)	lipoprotein(a)
MI	myocardial infarction
REVEAL	Randomized Evaluation of the Effects of Anacetrapib through Lipid modification
TRL	triglyceride-rich lipoprotein
VLDL	very-low-density lipoprotein

ultracentrifugation), non-HDL-C from 96 to 79 mg/dL (−18%), and Lp(a; lipoprotein(a)) by −25%. Although the outcome of REVEAL seems inconsistent with the previous negative trials, it is important to assess the differences in CETP inhibitors and trial design (Table). Dalcetrapib is a much less potent CETP inhibitor that raised HDL-C less and did not reduce LDL-C; furthermore, its trial dal-OUTCOMES was stopped early.³ The ACCELERATE (Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition with Evacetrapib in Patients with a High Risk for Vascular Outcomes) trial was performed with the potent CETP inhibitor evacetrapib which results in lipid changes similar to anacetrapib. However, ACCELERATE involved less than half the number of patients and cardiovascular disease (CVD) events, and was stopped early after ≈2.2 years for futility.⁴ In contrast, REVEAL was continued through its planned duration with a median follow-up of 4.1 years. The longer trial duration was likely of key importance because, similar to trials of other lipid-lowering drugs, the beneficial effects on CVD were greater after the first year of treatment with anacetrapib. Moreover, an exploratory analysis suggested that the benefit of anacetrapib increased with time as the trial proceeded. Thus, it is highly plausible that anacetrapib succeeded where other CETP inhibitors failed because of relative safety (compared with torcetrapib), potency (compared with dalcetrapib) and a study design that included adequate statistical power, and sufficiently long duration to uncover the benefit (compared with evacetrapib).

The demonstration of an overall antiatherogenic effect of CETP inhibition is buttressed by the majority of animal studies which have demonstrated a proatherogenic effect of CETP expression.⁸ Although studies in CETP transgenic mice have produced mixed results in atherosclerosis experiments, inhibition of CETP in rabbits, a species that naturally expresses CETP, have consistently shown reduced atherosclerosis, including in a CETP knockout rabbit which showed reduced aortic and coronary atherosclerosis when fed a high-cholesterol diet.¹⁰ Moreover,

multiple large human genetic studies have shown that single nucleotide polymorphisms (SNPs) in the CETP gene that are associated with increased HDL and reduced LDL-C are associated with reduced coronary heart disease (CHD).^{11–13} This includes SNPs that likely reduce the function of the promoter region upstream of the CETP gene,¹³ and most importantly CETP protein truncating mutations that abrogate the function of CETP.¹²

How Does CETP Inhibition Affect Plasma Lipoprotein Levels?

Before considering whether the benefit of anacetrapib was related to changes in HDL, LDL, or both, it is worth reviewing the mechanisms underlying the effects of CETP inhibition on plasma lipoprotein metabolism. The primary effect of CETP inhibition is a reduced rate of transfer of cholesteryl ester (CE) from HDL into TRLs (triglyceride-rich lipoproteins).^{14,15} This leads to an increased content of CE in HDL and the formation of larger HDL particles that are more slowly catabolized than normal. On the other side of the coin, CE is depleted in the TRL including in VLDL (very-low-density lipoprotein), chylomicrons, and their remnants.¹⁶ There is also a depletion of CE in LDL likely reflecting both diminished direct transfer from HDL, reduced amounts of CE in VLDL being converted into LDL CE and increased LDL particle catabolism (Figure). Thus, the major impact of CETP inhibition is an increase in HDL-C and a decrease in non-HDL-C (encompassing both cholesterol in TRL and LDL). Less obviously, the reduced transfer of CE from HDL to TRL also leads to a decrease in VLDL and LDL apoB levels. Careful metabolic studies in mildly hypercholesterolemic subjects treated with anacetrapib have shown that the reductions in VLDL and LDL apoB, as in genetic CETP deficiency, result from an increase in catabolism.^{17,18} In contrast, lowering of Lp(a) reflects a decrease in the production rate of apo(a).¹⁹ On a background of statin therapy, anacetrapib modestly lowered plasma triglyceride levels, reflecting an increase in VLDL triglyceride (TG) catabolism.²⁰

Because LDL catabolism is primarily mediated by LDLR (LDL receptor) mediated clearance in the liver, increased LDL catabolism in anacetrapib treated subjects likely reflects an increase in the clearance of LDL particles via the LDLR. This could result from a relative depletion of the regulatory cholesterol pool in the liver resulting from CETP inhibition and leading to an increase in LDLR mRNA (Figure). However, there was no increase in plasma lathosterol, which likely would have been increased as a result of increased sterol biosynthesis, if regulatory cholesterol pools in the liver were depleted.¹⁷ Thus, the authors speculated that the increased clearance of apoB could be caused by an increase in the affinity of LDL for its receptor, caused by changes in the properties of LDL particles, such as an increase in the LDL TG/CE ratio or an increase in the size or polydispersity of LDL particles (Figure). However, an increase in the numbers of hepatic LDLRs cannot be completely excluded because they were not directly measured. Studies in CETP transgenic mice have shown that CETP activity increases the cholesterol content in the liver and lowers the levels of the LDLR mRNA and protein, as well as HMGCoA (hydroxymethylglutaryl CoA) reductase mRNA, consistent with an increased content of the regulatory pool of cholesterol in the liver.²¹ This may reflect an increased

Table. Clinical Outcomes Trials of CETP Inhibitors

Trial (Drug)	Patients	Lipoprotein Changes	Duration	Outcome	Comments
ILLUMINATE (torcetrapib)	15 067 hi CV risk	HDL-C↑ 72% LDL-C↓*	1–2 y	↑CV events↑Death↑SBP (5 mm)	Electrolyte disturbances, hyperaldosteronism identified as off target effects*LDL measured indirectly
dal-OUTCOMES (dalcatrapib)	15 871 post ACS	HDL-C↑ ≈30% LDL-C→	31 mo	CV events→↑SBP (0.6 mm)	Trial stopped early for futility. Possible benefit in a genetic subgroup
ACCELERATE (evacetrapib)	12 092 hi risk vascular disease	HDL-C↑ 133% LDL-C↓*	26 mo	CV events→↑SBP (1.2 mm)	Trial stopped early for futility↓Deaths (not prespecified)*LDL measured indirectly
REVEAL (anacetrapib)	30 449 hi risk vascular disease	HDL-C↑ 104% LDL-C↓ 17%	4.1 y	↓Coronary events↑SBP (0.7 mm)	Trial went to planned completion↓new onset diabetes mellitus

ACCELERATE indicates Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition with Evacetrapib in Patients with a High Risk for Vascular Outcomes; ACS, acute coronary syndromes; CETP, cholesteryl ester transfer protein; CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; ILLUMINATE, The Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events Outcomes; LDL-C, low-density lipoprotein cholesterol; REVEAL, Randomized Evaluation of the Effects of Anacetrapib through Lipid modification; and SBP, systolic blood pressure.

efficiency of cholesterol transfer into hepatocytes resulting from transfer of CE from slowly turning over HDL particles into more rapidly cleared TRL remnants, or decreased channeling of HDL-C into biliary cholesterol bypassing the regulatory cholesterol pool. Whatever the precise mechanism, these studies strongly suggest that increased clearance of apoB lipoproteins via the LDLR pathway is occurring in subjects treated with potent CETP inhibitors, an effect that ultimately reflects the reduced rate of transfer of CE from HDL to TRL.

Is the CHD Benefit Related to Increased HDL or Decreased LDL/Non-HDL-C?

Formally, the only firm conclusion from REVEAL is that CETP inhibition resulted in a reduction in CV events as captured by the primary end point,⁵ and the mechanism of benefit is the subject of speculation. However, the mean reduction of non-HDL-C of 18% in REVEAL fell only slightly above the regression line relating the % reduction in CVD events to the absolute decrease in non-HDL-C, based on earlier studies with LDL lowering drugs, suggesting that the benefit may be largely explained by the reduction in non-HDL-C. However, these point estimates have substantial confidence intervals and also are based on an extrapolation of data that were mostly obtained at much higher levels of non-HDL-C. Moreover, there

may have been a small adverse effect related to blood pressure (BP) elevation in REVEAL, perhaps offsetting a beneficial effect of HDL changes. Overall, the conservative interpretation is that the benefit of anacetrapib was mostly or solely because of reduction in atherogenic lipoproteins; however, a contribution of HDL raising cannot be firmly excluded.

After the failure of torcetrapib, studies of HDL functionality were undertaken to exclude an adverse effect of CETP inhibition. These studies showed that in fact HDL from subjects treated with anacetrapib had enhanced ability to promote cholesterol efflux from cholesterol-loaded macrophages and preserved anti-inflammatory effects.²² Studies using an assay of HDL-C efflux capacity that had been validated as predicting coronary atherosclerosis and CHD in sizable population studies^{23,24} also showed that HDL from subjects treated with evacetrapib had increased cholesterol efflux capacity.²⁵ However, for unknown reasons the magnitude of this increase in subjects concomitantly treated with statins was surprisingly small (total cholesterol efflux capacity was increased by 21%) versus a larger increase in those receiving evacetrapib monotherapy (34%). Another possibility is that statin use reduces the expression of the ATP binding cassette transporters (ABCA1 and ABCG1) in macrophages, as result of decreased activity of the sterol-activated transcription factor LXR (liver X receptor), thereby offsetting the effects of increased HDL levels on macrophage cholesterol efflux. Further studies of HDL functionality in the context of CETP inhibition are warranted.

Is the Outcome of REVEAL Consistent With Insights From Human Genetics Studies?

Mendelian randomization studies of SNPs in multiple genes that are associated with changes in only HDL-C (but not triglycerides or LDL-C), for example in endothelial lipase (*LIPG*), have shown no association with CHD.²⁶ This has been interpreted as indicating that HDL-C is not in the causal pathway of atherosclerosis,²⁷ and suggests that decreased CHD associated with SNPs that reduce CETP expression or function are likely acting through changes in LDL-C (or non-HDL-C). Consistent with this interpretation, in the study of CETP truncating mutations, the magnitude of the benefit on CHD correlated well with the degree of LDL-C lowering.¹² However, variants in HDL-associated genes jointly account for very little of the variance in HDL-C levels and could have pleiotropic effects, weakening the general conclusion that HDL is not in the

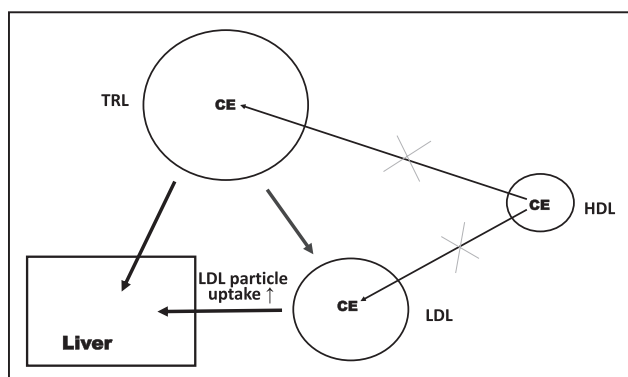


Figure. CETP (cholesteryl ester transfer protein) inhibition reduces LDL-C (low-density lipoprotein cholesterol) levels by 3 mechanisms: (1) decreased transfer of HDL (high-density lipoprotein) cholesteryl ester (CE) into (TRL) triglyceride-rich lipoproteins which are converted into LDL; (2) decreased transfer of HDL CE into LDL; and (3) increased uptake of LDL particles by the hepatic LDL receptor.

causal pathway of atherosclerosis. Adding to this complexity, there could be epigenetic effects masking a possible benefit of HDL raising genes. In this regard, a post hoc analysis of the dal-OUTCOMES trial has identified SNPs in the gene encoding adenylate cyclase 9 (*ADCY9*) as being associated with cardiovascular benefit in a subgroup of patients; a clinical trial (dal-GENE) in which dalcetrapib is being administered to high CV risk patients carrying the putative protective SNPs is ongoing.^{28,29} It will be of substantial interest to determine whether carriers of these variants had even better outcomes with anacetrapib in the REVEAL trial. Further analysis of CETP inhibitor clinical trial data, new assays of HDL functionality,^{30,31} as well as clinical outcomes studies based on infusion of reconstituted HDL particles that are highly active in promoting cholesterol efflux³² may provide additional insights into the complex relationship of HDL to atherosclerosis.

Is the Glass Half-Empty or Half-Full?

Despite achieving its primary end point, there may be concern that the benefit demonstrated by REVEAL was moderate and that the reduction in cardiovascular death was not significant. It is worth considering whether CETP inhibition is a mechanism with intrinsically limited benefit, or whether the result may have reflected aspects of the trial design. In general, the relationship between LDL lowering and its impact on CHD has shown that for every 40 mg/dL decrease in LDL-C, there is about a 25% reduction in CHD risk.³³ This implies that in a trial of LDL lowering, if patients in both placebo and active treatment groups are treated to very low LDL levels before randomization, the % reduction in CHD and the absolute benefit in the active treatment group will be less than they would have been if LDL levels were higher at randomization. This is because the % reduction in LDL-C (or non-HDL-C) will likely be similar at lower or higher starting LDL-C, so that the absolute reduction in LDL-C is greater when the starting LDL-C is higher and the risk reduction is accordingly larger. This supposition is supported by studies performed in a subset of patients in the DEFINE (Determining the Efficacy and tolerability of CETP inhibition with anacetrapib) trial which showed a larger absolute reduction in LDL-C by anacetrapib in patients with higher LDL-C at baseline compared with those with lower levels of LDL-C at baseline.³⁴ In REVEAL, the mean LDL-C at randomization was very low, 61 mg/dL. In part, this reflected the trial goal of achieving a prerandomization LDL-C <77 mg/dL by effective use of statins, but also the fact that people with total cholesterol >155 mg/dL after the statin run-in were intentionally excluded from the study. Notably, patients with non-HDL-C >101 mg/dL at randomization appeared to benefit more from anacetrapib than patients with non-HDL-C <85 mg/dL, with reductions in the rate ratio of MI+coronary death of 0.83 versus 0.96.⁵ In the clinical setting, patients with persistently elevated LDL or non-HDL-C on maximally tolerated statin therapy would be precisely those most likely to be treated with additional lipid-lowering agents. The implication could be that for people who would likely derive the greatest benefit, that is, with non-HDL-C >100 mg/dL after statin treatment, the clinical impact of anacetrapib could be considerably greater.

It is of interest to consider the results of REVEAL in the light of other recent trials of LDL lowering therapies that met their primary end points. There was a 6% reduction ($P<0.02$) in the primary cardiovascular end point in IMPROVE-IT (The Improved Reduction of Outcomes: Vytorin Efficacy International Trial) after 6 years of treatment with ezetimibe on top of statins.³⁵ In this trial, the mean LDL-C level in the statin only arm was slightly higher than in REVEAL (69.5 mg/dL) and reductions in LDL-C, non-HDL-C, and apoB were comparable to those obtained with atorvastatin. In contrast to evacetrapib, ezetimibe did not substantially increase HDL-C or lower Lp(a) levels. In the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) study in which evolocumab (a PCSK9 [proprotein convertase subtilisin/kexin type 9] mAb [monoclonal antibody]) was added to LDL lowering therapy with statins, the reduction in the primary end point was $\approx 15\%$. Compared with anacetrapib, there was a much more dramatic incremental LDL-C lowering of 61%. However, it also should be noted that in FOURIER the LDL-C was 92 mg/dL at entry reflecting the fact that the trial protocol stipulated that patients with already low LDL-C on statins (<70 mg/dL) were excluded from the study. Thus, the trial was more specifically designed to show a benefit of LDL lowering on CHD. Evolocumab lowered Lp(a) by $\approx 27\%$ and raised HDL-C by 8%. FOURIER was terminated after a mean of only 2.5 years and very likely the beneficial impact on CV events would have been larger had the study been continued for a longer time.

Devil Is in the Details: Safety and Side Effects

In REVEAL, anacetrapib treatment was devoid of major side effects, that is, involving cancer, infectious diseases, cognitive changes, depression, etc. Although not observed in a smaller preliminary safety trial,³⁶ there was a 0.7 mm increase in systolic blood pressure and 0.3 mm in diastolic blood pressure in anacetrapib treated subjects in REVEAL, similar in magnitude to what was observed with evacetrapib and dalcetrapib, but much less than for torcetrapib. Increased BP has not been reported in genetic CETP deficiency. However, this effect has been seen in multiple trials with different structural classes of CETP inhibitors strongly suggesting that it is mechanism based. The nature of this mechanism is unknown. For torcetrapib, hyperaldosteronism² and increased responses to endothelin in the vasculature³⁷ were shown, however, this occurred even in species that lack a CETP gene. Thus, relevance to subsequent CETP inhibitors is unlikely. Anacetrapib use was associated with a small increase in the proportion of patients with eGFR (estimated glomerular filtration rate) <60 mL/min at the end of the study, but there was no increase in albuminuria or serious adverse events attributed to renal failure. An increase in hemorrhagic stroke, as might be expected from increased BP and also as seen in a recent genetic study of CETP polymorphisms,³⁸ was not observed. The beneficial effect of CETP inhibition was observed across multiple prespecified subgroups. However, patients taking ACE inhibitors or angiotensin receptor blockers appeared to benefit less ($P<0.01$, unadjusted for multiple comparisons). Although this could represent a chance finding, in a small study an adverse impact of genetic CETP deficiency on CHD was reduced after adjustment for treatment

with nondiuretic antihypertensive drugs.³⁹ It is possible that treatment with ACE inhibitors marks a subgroup that had a more marked hypertensive response to CETP inhibition, or that inhibition of the renin-angiotensin system uncovers an adverse effect of CETP inhibition. Further investigation of a possible interaction between the use of antihypertensive drugs and CETP inhibitors are warranted.

Although several genetic studies have shown an association between CETP polymorphisms and age-related macular degeneration,^{40,41} there was no evidence for an increase in the onset or progression of retinal disease in REVEAL. This might reflect the differences between several years of pharmacological CETP inhibition versus lifelong genetic reduction in CETP deficiency; longer term monitoring will be needed to exclude macular degeneration as a possible adverse effect related to CETP inhibition. Anacetrapib has a very prolonged half-life because of accumulation in adipose tissue,⁴² a property that seems to be specific to anacetrapib and has not been seen with some other potent CETP inhibitors. Plasma levels of anacetrapib fall substantially after cessation of anacetrapib treatment, but the drug is persistent in adipose tissue for at least several years. Although no adverse effect has, to date, been linked to this property, it will be important to continue to monitor patients in REVEAL for potential consequences.

In REVEAL, the incidence of new onset diabetes mellitus was reduced by $\approx 10\%$, and there was a small reduction in HbA1c levels among nondiabetics. These beneficial effects on diabetes mellitus are consistent with previous reports of improvements in glucose/insulin ratios (HOMA-IR [homeostatic model assessment-insulin resistance]) and in HbA1c reported with torcetrapib⁴³ or evacetrapib (but not dalcetrapib),⁵ as well as the reductions in glucose levels seen in a study of subjects with CETP deficiency.³⁹ The mechanisms underlying the beneficial effects of CETP inhibitors on diabetes mellitus are poorly understood, but they contrast with the slight increase in diabetes mellitus and HbA1c associated with other mechanisms that lower LDL-C by upregulating the hepatic LDLR pathway, such as statins or genetic factors that reduce PCSK9.⁴⁴ Because these effects on diabetes mellitus are the opposite to those observed with other drugs increasing LDL clearance by the LDLR pathway, it is tempting to speculate that they may be related to the distinctively increased HDL levels resulting from CETP inhibition. Cholesterol accumulation in islet β -cells is associated with reduced insulin secretion in mice with knockouts of ABCA1/G1 in pancreatic β -cells likely reflecting decreased HDL-mediated cholesterol efflux.⁴⁵ However, statins would likely reduce β -cell cholesterol accumulation, so this is not an adequate explanation. There is high expression of CETP in insulin target tissues such as adipose and muscle,⁴⁶ raising the possibility of a local effect related to insulin sensitization. Finally, anacetrapib treatment on a background of statin therapy causes an increase in TG/apoB ratio of newly secreted TRL, reflecting decreased TG-CE interchange between TRL and HDL, and this TG enrichment of large TRL may increase susceptibility to lipoprotein lipase-mediated lipolysis.²⁰ Enhanced activity of lipoprotein lipase through various mechanisms is associated with decreased risk of both CHD and diabetes mellitus^{47,48} and this could

contribute to the decrease in diabetes mellitus associated with use of anacetrapib.⁵

Is There a Light at the End of the Tunnel?

The results of the REVEAL trial suggest that CETP inhibitors could represent a useful addition to the armamentarium of drugs currently being used to treat high-risk subjects intolerant to or not adequately treated with statins. The clinical use of evolocumab in patients who might benefit from this treatment has, to date, proven to be less than anticipated, in large part reflecting resistance from third party payers, and possibly from patients because of the need for subcutaneous injections. Thus, cost and convenience will likely be a major factor in the uptake of lipid-lowering therapies with incremental benefits over generic statins. As noted above, the side effect profile for anacetrapib is distinct from statins and PCSK9 deficiency, in particular the decrease in diabetes mellitus risk (although small) may be viewed beneficially by patients and physicians. Although the increase in mean BP is small, in individual patients it may be larger and BP would need to be closely monitored. Interestingly, CETP inhibitors seem to be more effective as monotherapy than when used with statins. The impact on both reducing apoB levels and on increasing cholesterol efflux capacity is substantially more (≈ 1.5 -fold– 2.0 -fold) when potent CETP inhibitors are used alone versus when they are added to statins.^{49,50} In earlier trials (Table), the degree of LDL-C lowering by CETP inhibitors was overestimated likely reflecting changes in apoB particle composition³⁴ and as a practical matter non-HDL-C should be used in the future to assess the effects of CETP inhibition.⁵¹ As monotherapy, the decreases in LDL-C and apoB are similar to the large effects on centrifugally separated LDL-C (-40%) and apoB (-35%) that were observed in complete genetic CETP deficiency.¹ This likely reflects the fact that CETP inhibition and statins both act in the same pathway to lower LDL apoB, that is, by increasing activity of the LDLR, limiting the incremental benefit of the CETP inhibitor. Thus, CETP inhibitors should be further evaluated for use as monotherapy, for example, in statin intolerant individuals. In summary, in a trial much larger and more than twice as long as previous trials, the CETP inhibitor anacetrapib was convincingly found to reduce coronary events. While ongoing monitoring and a careful review of safety is essential, anacetrapib could find its way to clinical use as another option for patients with coronary disease who require further reduction in LDL or non-HDL-C.

Note Added in Proof

Merck recently announced that they will not be submitting anacetrapib for Food and Drug Administration approval and marketing.

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