Cardiovascular outcomes trial with anacetrapib in subjects with high cardiovascular risk – are major benefits REVEALed?

Evaluation of HPS3/TIMI55-REVEAL Collaboration Group. Effects of anacetrapib in patients with atherosclerotic vascular disease. N Eng J Med 2017;377:1217-27.

1. Introduction
2. REVEAL
3. Expert opinion

Abstract

Introduction The actions of the cholesteryl ester transfer protein (CETP) inhibitors (torcetrapib, dalcetrapib and evacetrapib) include increasing high-density lipoprotein (HDL) cholesterol, but they do not reduce cardiovascular outcomes in subjects with high cardiovascular risk. Anacetrapib also inhibits CETP, increases HDL cholesterol and lowers low-density lipoprotein (LDL) cholesterol.

Areas Covered This evaluation is of the REVEAL (Randomized Evaluation of the Effects of Anacetrapib through Lipid Modification) trial, which was a cardiovascular outcomes trial with anacetrapib in subjects with high cardiovascular risk. Consideration is given as to whether increasing HDL cholesterol, lowering LDL cholesterol or other mechanisms/factors underlying the positive outcome with this CETP inhibitor.

Expert opinion After three years, the REVEAL trial with anacetrapib, demonstrated cardiovascular benefits, but not a reduction in coronary artery deaths. The reductions were not significant in years one and two. Thus, in my opinion, the benefits of anacetrapib were not major, and may not apply in ‘real’ world populations where adherence to medicines is lower than in REVEAL. Also, lowering LDL cholesterol and off-target mechanisms of anacetrapib, may have contributed to any beneficial and/or toxic effects. Anacetrapib has a good safety profile.

Key words, anacetrapib, cholesteryl ester transfer protein (CETP), cardiovascular clinical outcomes, dalcetrapib, evacetrapib, HDL cholesterol, LDL cholesterol, REVEAL, torcetrapib
1. Introduction

Despite the low-density lipoprotein (LDL) cholesterol-lowering statins reducing the mortality and morbidity associated with coronary artery disease, considerable mortality and morbidity remains in this disease. Low high-density lipoprotein (HDL) cholesterol levels (< 0.91 mmol/L) are also considered an independent risk factor for premature coronary disease. Epidemiology studies report, that in untreated subjects, an increase in HDL-cholesterol levels of 0.03 mmol/L is associated with a 2-4% reduction in the risk of cardiovascular disease [1]. As a result of these studies, it was considered that increasing HDL cholesterol levels with medicines might be useful in subjects with cardiovascular disease.

Larger increases in HDL cholesterol can be achieved by inhibiting cholesteryl ester transfer protein (CETP), and this can be achieved with the CETP inhibitors e.g. torcetrapib, anacetrapib, dalcetrapib, and evacetrapib. However, torcetrapib [2], dalcetrapib [3] and evacetrapib [4] have not been shown to improve cardiovascular outcomes to date. Thus, it is unclear whether a CETP inhibitor will be beneficial in cardiovascular disease.

Given that torcetrapib was shown to increase cardiovascular outcomes [2], it is probably not surprising that the development of anacetrapib has proceeded cautiously. In 2010, the Determining the Efficacy and Tolerability of CETP inhibition with Anacetrapib (DEFINE) study over 24 weeks, showed an increase HDL-cholesterol from 1.0 to 2.6 mmol/L, while decreasing LDL-cholesterol from 2.1 to 1.2 mmol/l. DEFINE was undertaken in 1623 subjects with coronary artery disease or at risk for coronary heart disease who were taking statins. Importantly, unlike torcetrapib, anacetrapib did not have the off-target effects of increasing blood pressure and aldosterone production. Although this was not a clinical outcomes trial, it was noted that anacetrapib was safe, as the cardiovascular events were similar in the anacetrapib (16/811, 2%) and placebo group (21/812, 2.6%) [5].

Subsequently, a phase 3 trial (the Randomized Evaluation of Anacetrapib Lipid-modifying therapy In patients with heterogenous familial hypercholesterolemia, REALIZE) showed major increases in HDL-cholesterol from 1.4 to 2.8 mmol/l and decreases in LDL-cholesterol from 3.3 to 2.1 mmol/l with anacetrapib over 52 weeks, in subjects that were taking statins. In REALIZE, there was no significant difference in cardiovascular events in the anacetrapib group (2/203, 2%), compared to the placebo group (0/102, 0%) [6], which again suggests that anacetrapib, is safe. Given this safety, it was important to undertake a large clinical outcomes trial to determine whether anacetrapib is efficacious, and this is the REVEAL (Randomized Evaluation of the Effects of Anacetrapib through Lipid Modification) [7] trial. Although REVEAL showed some positive clinical outcomes with anacetrapib, Merck (MSD) have decided not to submit applications for regulatory approval of anacetrapib, but have not elaborated on the reasons for this [8]. This evaluation is of REVEAL, and as part of the expert opinion, considers why anacetrapib is no longer being developed.

2. REVEAL [7]

2.1 Methods and results

Although Merck funded and collaborated in REVEAL, it was designed and conducted by the British Heart Foundation and Medical Research Council. REVEAL was performed at 431 sites in Europe, North America and China.
To be eligible, subjects has to be > 50 years old, and have a history of myocardial infarction, cerebrovascular atherosclerotic disease, peripheral-artery disease, or diabetes with symptomatic coronary heart disease. Exclusions included recent coronary event or stroke, planned coronary revascularization, and clinically significant liver and kidney disease. Subjects were also excluded if they were taking a fibrate or niacin, or were poorly adherent to clinic visits or medications. Prior to randomization, subjects were administer atorvastatin in an attempt to reduce LDL cholesterol below 2 mmol/L for 8 to 12 weeks, and then were excluded if they had total cholesterol > 4.0 mmol/L.

REVEAL enrolled 30,449 subjects, to either anacetrapib (100 mg) or placebo. Most of the subjects were in Europe (52%; North America, 20%; China, 28%), with a mean age of 67 years, and 84% were male. Most subjects had coronary heart disease (88%), and some had diabetes (37%) and/or cerebrovascular disease (22%).

The primary outcome was the first major coronary event, and was a composite of coronary death, myocardial infarction, or coronary revascularization, and this occurred in significantly fewer subjects in the anacetrapib group (10.8%; 1640/15225) than in the placebo group (11.8%; 1803/15224; P = 0.004) with a median duration of follow-up was 4.1 years. Of the components of the primary outcome, myocardial infarction (anacetrapib, 4.4% vs 5.1%) and coronary revascularization (7.1% vs 7.9%), but not coronary deaths, were significantly reduced. However, there was no benefit in the primary outcome in years one (3.1% in both groups), two (2.7% in anacetrapib group vs 2.8% in the placebo group) or three (2.6% vs 3.0%). The primary outcome only became significant when years > 1 were combined significant (8.0% in the anacetrapib group vs 9.1% in the placebo group) or all the years were combined (10.8% vs 11.8%).

The secondary outcome was the composite of myocardial infarction, coronary death, or presumed ischemic stroke and this was not significantly different between the groups, with the presumed ischemic strokes being the same in both groups (3.2%). There was also no difference in the rates of hospitalization for heart failure between the anacetrapib and placebo group.

At the trial midpoint, HDL cholesterol was higher by 1.12 mmol/L (104%) and the LDL cholesterol was lower by 0.68 mmol/L (41%) in the anacetrapib, compared to the placebo group. Adherence to both anacetrapib and the statins was very high in REVEAL (≥ 85%).

There were no differences in rates of death, cancer, macular degeneration, liver disorders, or mood or cognitive function between the anacetrapib and placebo groups. The incidence of new-onset diabetes was lower in the anacetrapib than placebo group; 5.3% vs 6.0%, P = 0.0495. With regard to adverse events, there were no significant differences, with two exceptions; at the beginning of the study, the percentage of subjects with glomerular filtration rates < 60 ml/min/1.73 m² was similar in the anacetrapib and placebo groups (10.9% vs 11.2%, respectively) but at the end of the study, the percentage was higher in the anacetrapib (11.5%) than in the placebo group (10.6%). Also, the blood pressures were matched at the start of the study, but at the end of the study, the systolic and diastolic blood pressures were 0.7 and 0.3 mmHg higher, respectively, in the anacetrapib than the placebo group.

2.2 Discussion
In their discussion, the authors consider why their trial showed benefit with anacetrapib when previous trials with other CETP-inhibitors had not. Thus, they consider that the off-target effects of torcetrapib may have caused the excess risks of cardiovascular events in ILLUMINATE [2], and point out that the 0.7 mmHg in systolic blood pressure with anacetrapib was much lower than the 5 mmHg with torcetrapib. The authors also considered that stopping the studies with dalcetrapib (dai-OUTCOMES [3]) and evacetrapib (ACCELERATE [4]) after 2 years may have contributed to their lack of efficacy [7].

Also, the authors point out that the cardiovascular benefits observed with anacetrapib are consistent with other studies showing cardiovascular benefits with similar reductions in LDL cholesterol as with anacetrapib in REVEAL. As a consequence, the benefits of anacetrapib may have been due to lowering LDL cholesterol, and it is not known whether the increase in HDL cholesterol contributed to the cardiovascular benefits with anacetrapib in REVEAL [7].

Anacetrapib accumulates in adipose tissue, and although plasma levels fall substantially shortly after stopping treatment, the levels in the adipose tissue decline minimally over one year, and slow the further fall in plasma levels [9]. This is the reason, the authors cite for continuing to monitor the efficacy and safety of anacetrapib for a further two years [7].

### 2.3 Conclusion

The REVEAL cardiovascular outcomes trial with anacetrapib demonstrated cardiovascular benefits with a good safety profile [7].

### 3. Expert opinion

#### 3.1 Exclusions and validity of REVEAL to real populations

To my knowledge, it is unusual for subjects to be monitored for adherence prior to a clinical trial and for subjects with known poor adherence to medication to be excluded. However, this has happened in REVEAL. As a consequence, the adherence to both anacetrapib and the statins was very high in REVEAL (≥ 85%). Previously studies have demonstrated that there is a wide range in adherence to statins, and that adverse cardiovascular outcomes are higher in those with poor statin adherence [10]. Presumably, the benefit observed with anacetrapib in REVEAL is dependent on these high levels of adherence to both statins and anacetrapib. Thus, it is possible that the benefits of anacetrapib may not apply to real populations, where the adherence levels are lower.

There is no mention of excluding subjects with poor adherence in the ILLUMINATE study with torcetrapib [2], the dai-OUTCOMES trial with dalcetrapib [3] or the ACCELERATE trial with evacetrapib [4], and no reports of adherence rates in these studies. Thus, the results of these studies, in contrast to REVEAL, may reflect their effects in subjects with a range of adherence levels.

In the supplementary information for REVEAL, it states that of the 33426 subjects that entered the randomization visit, 2977 were excluded from randomization, with 2971 meeting at least one exclusion criteria. These exclusion criteria include not adhering to the atorvastatin or not getting the required reduction in total cholesterol to 4.0 mmol/l in 8-12 weeks of pre-randomization. This exclusion criterion in REVEAL relating to reduction in total cholesterol is not so unusual, as similar
exclusion occurred in ILLUMINATE with torcetrapib [2] and ACCELERATE with evacetrapib [4], but not dal-OUTCOMES with dalcetrapib [3].

As the results of clinical outcome trials are only valid for the population enrolled, it is not known whether anacetrapib will be of any benefit to subjects who are poorly adherent or have high cholesterol despite taking atorvastatin.

3.2 No list of other drugs used provided

All of the significant differences in the anacetrapib and placebo groups were small and thus it is important that the groups are perfectly matched other than for anacetrapib. As no list of other drugs used at the start/baseline or at the end of the REVEAL study is provided, it is not known whether these drugs were matched at the start or finish. Changes in other drug use during the study could have contributed to the changes in cholesterol levels and the cardiovascular benefits or the increased blood pressure apparently observed with anacetrapib. In my opinion, lists of other drugs being used should be supplied in clinical trials with new drugs to eliminate this possibility.

3.3 Blood pressure increases

Like anacetrapib, torcetrapib [2] and evacetrapib [4] also cause major reductions in LDL cholesterol, but unlike anacetrapib, do not cause cardiovascular benefit. Dalcetrapib causes a much lower reduction in LDL cholesterol than the other CETP inhibitors, and is also ineffective in reducing cardiovascular outcomes [3]. It has been postulated that detrimental effects may counter any benefits due to reducing LDL cholesterol or increasing HDL cholesterol with the CETP inhibitors. One possible detrimental effect is increased blood pressure as torcetrapib, evacetrapib and dalcetrapib increase systolic blood pressure by 5.4 mm Hg [2], 1.2 mmHg [4], and 0.6 mmHg [3], respectively. Anacetrapib also increased systolic blood pressure by 0.7 mmHg, but does have cardiovascular benefits [7]. Thus, it seems unlikely that increasing blood pressure counters any benefits of lipid modification with evacetrapib and, possibly, dalcetrapib. However, as torcetrapib has a much larger effect on blood pressure than the other CETP inhibitors, the increase in blood pressure may have countered any potential benefits of modifying lipids with this agent.

3.4 CETP, HDL cholesterol and cardiovascular disease

As discussed previously, although anacetrapib increases the levels of HDL cholesterol, it may be the lowering of LDL cholesterol that accounts for its cardiovascular benefit [7]. Combined with the failure of other CETP inhibitors (torcetrapib, dalcetrapib and evacetrapib), agents that increase HDL cholesterol, to improve cardiovascular outcomes in subjects at high risk, research should turn back to the relationship between CETP, HDL cholesterol and cardiovascular disease.

CETP is secreted predominantly from the liver and circulates in the plasma, mainly bound to HDL cholesterol. CETP promotes the transfer of cholesteryl esters from HDL cholesterol to apolipoprotein (apo) B-containing lipoproteins in exchange for triglycerides. Genetic studies show that low CETP levels are associated with higher HDL cholesterol, lower LDL cholesterol and lower triglyceride, and that this was associated with a lower risk of cardiovascular disease [11]. However, to date, we have a poor understanding of the consequences of inhibiting CETP in humans, as clinical trials with torcetrapib, dalcetrapib and evacetrapib did not show reduced cardiovascular events [12].
For LDL cholesterol, there is good evidence from human genetic studies and clinical trials that plasma levels are causally related to cardiovascular disease. However, this is not so for HDL cholesterol. Thus, mendelian genetic analysis has shown no causal link between plasma HDL cholesterol levels and ischemic heart disease and the risk of myocardial infarction [13,14]. From clinical trials, a 2014 meta-analysis of 117,411 subjects who were taking niacin, fibrates or CETP inhibitors to increase HDL cholesterol, was unable to show any benefits on all-cause mortality, coronary heart disease mortality, myocardial infarction, or stroke in subjects treated with statins [15]. Recently, epidemiology evidence has suggested that very high HDL cholesterol levels may actually increase mortality [16]. This is clear evidence that the relationship between HDL cholesterol and cardiovascular disease requires further investigation, and questions whether raising HDL cholesterol is an appropriate target in subjects being treated with statins.

### 3.5 An off-target beneficial effect of anacetrapib - proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition

The authors of REVEAL provided evidence that it may be the lowering of LDL cholesterol that may account for the cardiovascular benefits of anacetrapib [7]. Although they implied that the lowering of LDL cholesterol was due to CETP inhibition [7], other mechanisms can lead to reduced LDL cholesterol e.g. PCSK9 reduction.

One of the causes of familial hypercholesterolemia is a mutation in the genes encoding PCSK9 (PCSK9). Anacetrapib has been shown to decrease (PCSK9) expression and plasma levels, and this was associated with reduced LDL cholesterol in mice [17]. Thus, in familial hypercholesterolemia, any benefits of anacetrapib could be due to a decrease in PCSK9, rather than CETP, or decreasing both. However, no benefits have been shown in this condition with anacetrapib, to date. Hopefully, the REALIZE study in subjects with familial hypercholesterolemia is continuing to answer this question.

Given that reducing LDL cholesterol with the PCSK9 inhibitor evolocumab reduced cardiovascular events in subjects with cardiovascular disease [18], it is possible that inhibition of PCSK9 with anacetrapib in REVEAL may have contributed to its small beneficial effect.

### 3.6 Other off-target effects of anacetrapib

Despite rats lacking the CETP gene; anacetrapib, torcetrapib and dalcetrapib, increased phenylephrine-induced contractions of isolated small mesenteric vessels. The processes involved were redox-sensitive, and signal transducer and activator of transcription 3 (STAT-3)-dependent [19].

In CETP-transgenic mice, despite major increases in HDL cholesterol, anacetrapib impaired endothelium function [20]. Given that this unfavourable effect is not observed with evacetrapib, it is possible that this detrimental effect on anacetrapib is not related to inhibiting CETP, and could be counteracting any potential benefit of inhibiting CETP with anacetrapib humans.

### 3.7 Why have Merck stopped the development of anacetrapib?

Although Merck have stopped the development of anacetrapib [8], they have not elaborated on the reasons for this. This information would be potentially valuable to scientists and clinicians involved in understanding lipid metabolism and developing drugs to prevent lipid-related diseases.
pointed out by the authors of REVEAL, the cardiovascular benefits observed with anacetrapib are consistent with other studies showing cardiovascular benefits with similar reductions in LDL cholesterol [7]. My speculation is that the Merck would have difficulty registering anacetrapib as its beneficial effects are probably primarily related to lowering LDL cholesterol, rather than to increasing HDL cholesterol or any other mechanisms.

3.8 Cardiovascular outcomes trial with anacetrapib – are major benefits REVEALed?

The REVEAL cardiovascular outcomes trial with anacetrapib demonstrated cardiovascular benefits, but these were not major, in my opinion. Thus, there was no benefit in primary outcome in years one, two or three alone, and it was only when the years > one were combined, that the cardiovascular benefit became significant. Even then the benefit was only in myocardial infarction and coronary revascularization, and did not extend to coronary deaths.

3.9 Is this the end for the CETP inhibitors?

There is no evidence from REVEAL that increasing the levels of HDL cholesterol by inhibiting CETP is the mechanism underlying the beneficial effects of anacetrapib. Coupled with the fact that the other HDL cholesterol increasing CETP inhibitors, which have been subjected to major clinical outcomes have not shown clinical benefits (see Introduction), it is not surprising that the development of torcetrapib was stopped by Pfizer in 2007, dalcetrapib by Hoffman-La Roche in 2012, evacetrapib by Eli Lilly in 2015, and anacetrapib by Merck in 2017 [8]. There are also no recent reports of ongoing development of other CETP inhibitors in the earlier phases of clinical trials; CDK-519, DRL-17822 or obicetrapib (TA-8995) [21]. Thus, it is likely that we have reached the end of the development of CETP inhibitors for use in the prevention of cardiovascular outcomes. Focus should now be on basic research to identify other targets that may prevent cardiovascular outcomes.

References

1. Gordon DJ, Probstfield JL, Garrison RJ et al. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. Circulation 1989;79:8-15.
2. Barter PJ, Caulfield M, Eriksson M et al. Effects of torcetrapib in patients at high risk of coronary events. N Engl J Med 2007;2109-22.
   • Important clinical cardiovascular trial showing detrimental events with torcetrapib in subjects at high risk of cardiovascular events
3. Schwartz GG, Olsson AG, Abt M et al. Effects of dalcetrapib in patients with a recent acute coronary syndrome. N Engl J Med 2012;367:2089-99.
   • Major clinical cardiovascular trial showing no benefit with dalcetrapib in subjects with a recent coronary syndrome
4. Lincoff AM, Nicholls SJ, Riesmeyer JS et al. Evacetrapib and cardiovascular outcomes in high-risk vascular disease. N Engl J Med 2017;376:1933-42.
   • Important clinical cardiovascular trial showing no benefit with evacetrapib in subjects at high risk of cardiovascular events
5. Cannon CP, Shah S, Dansky HM et al. Safety of anacetrapib in patients with or at high risk for coronary heart disease. N Engl J Med 2010;363:2408-15.
   • Trial demonstrating safety of anacetrapib in subjects at high cardiovascular risk
6. Kastelein JJ, Besseling J, Shah S et al. Anacetrapib as lipid-modifying therapy in patients with heterozygous familial hypercholesterolaemia (REALISE): a randomised, double-blind, placebo-controlled, phase 3 study. Lancet 2015;385:2163-61.
7. HPS3/TIMI55-REVEAL Collaboration Group. Effects of anacetrapib in patients with atherosclerotic vascular disease. N Engl J Med 2017;377:1217-27.
   • Recent clinical cardiovascular trial showing limited benefits of anacetrapib in subjects at high cardiovascular risk
8. Merck.com Merck provides update on anacetrapib development program. [Cited 2018 Feb 8] http://investors.merck.com/news/press-release-details/2017/Merck-Provides-Update-on-Anacetrapib-Development-Program/default.aspx
9. Gotto AM, Cannon CP, Li XS et al. Evaluation of lipids, drug concentration, and safety parameters following cessation of treatment with the cholesteryl ester transfer protein inhibitor anacetrapib in patients with or at high risk for coronary heart disease. Am J Cardiol 2014;113:76-63.
10. de Vera M, Bhole V, Burns LC, Locaille D. Impact of statin adherence on cardiovascular disease and mortality outcomes: a systematic review. Br J Clin Pharmacol 2014;78:684-98.
11. Nomura A, Won HH, Khera AV et al. Protein-truncating variants at the cholesteryl ester transfer protein gene and risk for coronary heart disease. Circ Res 2017;121:81-88.
12. Hovingh GK, Ray KK, Boekholdt SM. Is cholesteryl ester transfer protein inhibition an effective strategy to reduce cardiovascular risk? CETP as a target to lower CVD risk: Suspension of disbelief. Circulation 2015;132:433440.
13. Frikke-Schmidt R, Nordestgaard BG et al. Association of loss-of-function mutations in the ABCA1 gene with high-density lipoprotein cholesterol levels and risk of ischemic heart disease. JAMA 2008;290:2524-32.
14. Voight B, Peloso GM, Orho-Melander M et al. Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study. Lancet 2012;380:572-80.
15. Keene D, Price C, Shun-Shin MJ, Frances DP. Effect on cardiovascular risk of high density lipoprotein targeted drug treatments niacin, fibrates, and CETP inhibitor: meta-analysis of randomised controlled trials including 117,441 patients. BMJ 2014;349:g4379. doi: 10.1136/bmj.g4379.
   • Meta-analysis showing that increasing HDL cholesterol is not beneficial in subjects taking statins
16. Masen CM, Varbo A, Nordestgaard BG. Extreme high high-density lipoprotein cholesterol is paradoxically associated with high mortality in men and women: two prospective cohort studies. Eur Heart J 2017;38:2478-86.
17. van der Tuin SJ, Kühnast S, Berbée JF et al. Anacetrapib reduces (V)LDL cholesterol by inhibition of CETP activity and reduction of plasma PCSK9. J Lipid Res 2015;56:2085-93.
   • Preclinical investigation showing relevant off-target effect of anacetrapib
18. Sabatine MS, Giugliano RP, Keech AC et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017;376:1713-22.
   • Major clinical trial showing clinical benefits with evolocumab, a PCSK9 inhibitor
19. Rios FJ, Lopes RA, Neves KB, Camargo LL, Montezano AC, Touyz RM. Off-target vascular effects of cholesteryl ester transfer protein inhibitors involve redox-sensitive and signal transducer and activation of transcription 3-dependent pathways. J Pharmacol Exp Ther 2016;357:415-22.
20. Simic B, Mocharia P, Crucet M et al. Anacetrapib, but not evacetrapib, impairs endothelium function in CETP-transgenic mice in spite of marked HDL-C increase. Atherosclerosis 2017;257:186-94.
21. Adis. Obicetrapib – Amgen [Cited 2018, Feb 12] http://adisinsight.springer.com/drugs/800029292