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Is there a future for CETP-inhibitor therapy?

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"Given the excess mortality caused by torcetrapib, it is unlikely that any CETP inhibitor will receive regulatory approval prior to the completion of the long-term cardiovascular end point trials..."

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Despite large improvements in cardiovascular disease mortality, coronary heart disease (CHD) and stroke remain the leading causes of death in most nations around the world [1,101]. Statins are the foundation for cardiovascular prevention, with up to 50% reductions in cardiovascular risk with the more potent statins [2]. In both statin-treated and -untreated patients, low levels of high-density lipoprotein cholesterol (HDL-C) are an important predictor of subsequent cardiovascular risk [3,4]. In epidemiologic studies, each 1 mg/dl (0.03 mmol, or ~2–3%, depending on baseline HDL-C level) increase in HDL-C is associated with a 2–4% reduction in the risk of CHD events, independent of low-density lipoprotein cholesterol (LDL-C) levels [5].

Of the drugs currently on the market, niacin is the most effective at raising HDL-C (~25% at the 2-g dose), while statins and fibrates have more modest HDL-C-raising effects (3–10%) [6]. However, it is not clear that pharmacologically raising HDL-C *per se* with these agents reduces cardiovascular risk. A meta-analysis of HDL-C-raising drugs found that after adjusting for LDL-C-lowering, raising HDL-C (or lowering triglycerides) was not associated with further cardiovascular risk reduction [6].

Several classes of HDL-C-raising agents with novel mechanisms of action are under development [7]. Farthest along are the cholesteryl ester transfer protein (CETP) inhibitors. CETP mediates the transfer of cholesteryl esters from HDL to proatherogenic apolipoprotein B-lipoproteins for transportation of cholesterol back to the cells; blocking CETP increases levels of mature HDL-C particles. The first CETP inhibitor to move into clinical trials was torcetrapib (Pfizer, Inc). Despite large increases in HDL-C, development of torcetrapib was terminated due to excess mortality in the torcetrapib group of the large outcomes trial, Investigation of Lipid Level management to Understand its Impact in Atherosclerotic Events (ILLUMINATE). Increased mortality in the torcetrapib-treated group occurred despite a 72% increase in HDL-C and a 25% decrease in LDL-C [8]. Torcetrapib also had no benefit on atherosclerotic progression in two noninvasive imaging studies, despite similar lipid changes [9,10]. The adverse mortality effect of torcetrapib has been largely attributed to accelerated hypertension due to activation of the renin–angiotensin–aldosterone system through a non-CETP-dependent effect [11]. Other mechanisms, such as lack of HDL functionality and proinflammatory effects, have also been proposed to explain torcetrapib's adverse effects.

Two CETP inhibitors are still in development, anacetrapib and dalcetrapib. Neither agent has been found to increase blood pressure or influence the renin–angiotensin–aldosterone axis in studies to date [7]. The more potent CETP inhibitor, anacetrapib, comes from the same chemical class as torcetrapib and strongly binds to the CETP molecule. Added to optimal statin therapy, anacetrapib 100 mg has been shown to increase HDL-C by 138% and reduce LDL-C an additional 40%, with modest triglyceride-lowering effects [12]. The less potent dalcetrapib is from a different chemical class, binds reversibly to and induces a different conformational

change in CETP. Dalcetrapib 600 mg added to statin therapy increases HDL-C by 25–30% with minimal effects on LDL-C or triglycerides [7].

Several large outcomes trials of HDL-C-raising agents are ongoing (Table 1) [7,13,102–104]. Some indication of the benefits of raising HDL-C will come from two ongoing trials of niacin added to statin therapy, with anticipated completion dates in 2012 to 2013 [103,104]. It should be noted that the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial found no additional cardiovascular risk reduction when fenofibrate was added to simvastatin therapy in diabetic patients, although there was a trend toward benefit in those with the lowest HDL-C and highest triglyceride levels [14]. However, in the trial as a whole, minimal changes in LDL-C or HDL-C were observed in the fenofibrate group; lipid changes were not reported for the subgroup analysis.

Why might raising HDL-C with CETP inhibitors be beneficial? Reverse cholesterol transport has been thought to be the primary cardiovascular benefit of HDL. Removal of free cholesterol from peripheral macrophages contributes to the cholesterol accumulation that is the hallmark of the transformation of apolipoprotein AI into the mature HDL molecule. Mature HDL transports cholesterol to the liver for reuptake or incorporation into bile acids for excretion [15]. Although dalceptrapib (but not anacetrapib or torcetrapib) has been shown to increase fecal sterol elimination in hamsters, drug-induced excretion of cholesterol into the feces has been poorly documented in humans [16,17]. However, it is unclear whether differences in reverse cholesterol transport are an important influence in atherogensis. Dalcetrapib was shown to inhibit atherosclerosis progression in normocholesterolemic, but not hypercholesterolemic rabbits [18,19], whereas torceptrapib was shown to inhibit atherosclerosis in hypercholesterolemic rabbits, but not in humans [9,10,20]. However, a *post hoc* analysis of the Investigation of Lipid level Management Using Coronary Ultrasound to Assess reduction of Atherosclerosis by CETP Inhibition and HDL Elevation (ILLUSTRATE) trial found that atherosclerotic regression was observed with very high HDL-C levels of >85 mg/dl, suggesting that very high levels of HDL-C could overcome torcetrapib's harmful effects [21].

"...while HDL-C levels are an important indicator of increased cardiovascular risk, it remains unknown whether pharmacologically raising HDL-C *per se* will decrease cardiovascular risk."

Why might raising HDL-C with CETP-inhibitors not be beneficial? Several gene variants associated with lower HDL-C levels, including several CETP polymorphisms, are not associated with increased cardiovascular risk [7,17]. Although HDL has been shown to have antioxidant and anti-inflammatory effects that promote vasodilation and reduce thrombosis, HDL in individuals with cardiovascular disease is often dysfunctional and proinflammatory [17]. While it could be that increasing dysfunctional HDL is not beneficial, it does not appear that torcetrapib induced HDL dysfunction [22]. Indeed, some of the alterations in HDL

Table 1. Ongoing trials of high-density lipoprotein cholesterol-raising agents.

Study (clinicaltrials.gov identifier)	Study treatment (study population)	Primary end point (anticipated completion)	Ref.
Dal-OUTCOMES (NCT0c0658515)	Dalcetrapib vs placebo; recent acute coronary syndrome; statin treated (n = 15,000)	Major cardiovascular events (2013)	[13]
Dal-VESSEL (NCT00655538)	Dalcetrapib vs placebo; CHD or CHD equivalent; statin treated (n = 450)	Endothelial function and blood pressure (2011)	[105]
Dal-PLAQUE (NCT00655473)	Dalcetrapib vs placebo; CHD or CHD equivalent; statin treated to LDL-C <100 mg/dl (n = 100)	PET/CT and MRI-defined atherosclerotic plaque (2011)	[106]
Dal-PLAQUE2 (NCT01059682)	Dalcetrapib vs placebo; cardiovascular disease; statin treated (n = 900)	Carotid intimal thickness and intracoronary vascular ultrasound techniques (2013)	[107]
REVEAL (NCT01252953)	Anacetrapib vs placebo; cardiovascular disease; statin treated (n = 30,000)	Major cardiovascular events (2017)	[102]
AIM-HIGH (NCT 00120289)	Extended-release niacin 2 g vs placebo; cardiovascular disease; statin treated (n = 3414)	Major cardiovascular events (2012)	[103]
HPS-2 THRIVE (NCT00461630)	Extended-release niacin 2 g + laropiprant vs placebo; cardiovascular disease; statin treated to LDL-C <100 mg/dl (n = 25,673)	Major cardiovascular events (2013)	[104]

AIM-HIGH: Niacin Plus Statin to Prevent Vascular Events; HPS-2 THRIVE: Treatment of HDL to Reduce the Incidence of Vascular Events; REVEAL: Randomized Evaluation of the Effects of Anacetrapib Through Lipid Modification.

structure may favor improvements in anti-atherogenic functionality. In addition, dalcetrapib has been shown to improve endothelial function in the subgroup of patients with baseline HDL-C levels <46 mg/dl (<1.19 mmol/l), but not in those with higher HDL-C levels, who had better endothelial function at baseline [23]. On the other hand, torcetrapib, anacetrapib and dalcetrapib have all been shown to increase highly sensitive C-reactive protein (CRP), a summary measure of inflammation associated with increased cardiovascular risk. Anacetrapib increased CRP from baseline by 10% after 24 weeks and by 18% after 76 weeks compared with placebo; dalcetrapib increased CRP by 30% after 24 weeks, and 29% after 48 weeks [24,25]. Although torcetrapib did not increase CRP at 12 weeks in the ILLUMINATE trial or at 24 months in the Rating Atherosclerotic Disease Change by Imaging with a New CETP Inhibitor (RADIANCE) trial, CRP did increase 20% at 24 months in the ILLUSTRATE trial [8–10].

In conclusion, while HDL-C levels are an important indicator of increased cardiovascular risk, it remains unknown whether pharmacologically raising HDL-C *per se* will decrease cardiovascular risk. The results of ongoing noninvasive imaging and cardiovascular end point trials evaluating dalcetrapib and anacetrapib will determine if raising HDL-C via CETP inhibition is an effective strategy for reducing cardiovascular events. Given the excess mortality caused by torcetrapib, it is unlikely that any CETP inhibitor will receive regulatory approval prior to the completion of the long-term cardiovascular end point trials, regardless of impressive reduction in LDL-C or increases in HDL-C over statin therapy.

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Bibliography

1 Roger VL, Go AS, Lloyd-Jones DM *et al.* Heart disease and stroke statistics – 2011 update: a report from the American Heart Association. *Circulation* 123(4), e18–e209 (2010).

2 Cholesterol Treatment Trialists Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 376 1670–1681 (2010).

3 Barter P, Gotto AM, LaRosa JC *et al.* HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. *N. Engl. J. Med.* 357, 1301–1310 (2007).

4 National Cholesterol Education Program Expert Panel on Detection, E.a.T.o.H.B.C.i.A. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 106, 3143–3421 (2002).

5 Gordon DJ, Probstfield JL, Garrison RJ *et al.* High-density lipoprotein cholesterol and cardiovascular disease: four prospective american studies. *Circulation* 79, 8–15 (1989).

6 Briel M, Ferreira-Gonzalez I, You JJ *et al.* Association between change in high density lipoprotein cholesterol and cardiovascular disease morbidity and mortality: systematic review and meta-regression analysis. *BMJ* 338, b92 (2009).

7 Robinson JG. Dalcetrapib: a review of Phase II data. *Expert Opin. Investig. Drugs* 19, 795–805 (2010).

8 Barter PJ, Caulfield M, Eriksson M *et al.* Effects of torcetrapib in patients at high risk for coronary events. *N. Engl. J. Med.* 357, 2109–2122 (2007).

9 Kastelein JJ, van Leuven SI, Burgess L *et al.* Effect of torcetrapib on carotid atherosclerosis in familial hypercholesterolemia. *N. Engl. J. Med.* 352, 1425–1435 (2007).

10 Nissen SE, Tardif JC, Nicholls SJ *et al.* Effect of torcetrapib on the progression of coronary atherosclerosis. *N. Engl. J. Med.* 356, 1304–1316 (2007).

11 Tall AR, Yvan-Charvet L, Wang N. The failure of torcetrapib: was it the molecule or the mechanism? *Arterioscler. Thromb. Vasc. Biol.* 27, 257–260 (2007).

12 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.* 363, 2406–2415 (2010).

13 Schwartz GG, Olsson AG, Ballantyne CM *et al.* Rationale and design of the dal-OUTCOMES trial: efficacy and safety of dalcetrapib in patients with recent acute coronary syndrome. *Am. Heart J.* 158, 896–901 (2009).

14 Januszkiewicz L. The Accord Study Group. Effects of combination lipid therapy in Type 2 diabetes mellitus. *Kardiol Pol.* 68(7), 853–854 (2010).

15 Lewis G, Rader D. New insights into the regulation of HDL metabolism and reverse cholesterol transport. *Circ. Res.* 96, 1221–1232 (2005).

16 Niesor E, Okamoto H, Maugeais C *et al.* The effects of dalcetrapib on macrophage reverse cholesterol transport in a rodent model. *Circulation* 120, S468 (2009) (Abstract).

17 Vergeer M, Holleboom AG, Kastelein JJ, Kuivenhoven JA. The HDL hypothesis: does high-density lipoprotein protect from atherosclerosis? *J. Lipid Res.* 51(8), 2058–2073 (2010).

18 Okamoto H, Yonemori F, Wakitani K, Minowa T, Maeda K, Shinkai H. A cholesteryl ester transfer protein inhibitor attenuates atherosclerosis in rabbits. *Nature* 406, 203–207 (2000).

19 Huang Z, Inazu A, Nohara A, Higashikata T, Mabuchi H. Cholesteryl ester transfer protein inhibitor (JTT-705) and the development of atherosclerosis in rabbits with severe hypercholesterolaemia. *Clin. Sci.* 103, 587–594 (2002).

20 Morehouse LA, Sugarman ED, Bourassa PA *et al.* Inhibition of CETP activity by torcetrapib reduces susceptibility to diet-induced atherosclerosis in New Zealand white rabbits. *J. Lipid Res.* 48, 1263–1272 (2007).

21 Nicholls SJ, Tuzcu EM, Brennan DM, Tardif JC, Nissen SE. Cholesteryl ester transfer protein inhibition, high-density lipoprotein raising, and progression of coronary atherosclerosis. Insights from ILLUSTRATE (Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation). *Circulation* 118, 2506–2514 (2008).

22 Chapman MJ, Le Goff W, Guerin M, Kontush A. Cholesteryl ester transfer protein: at the heart of the action of lipid-modulating therapy with statins, fibrates, niacin, and cholesteryl ester transfer protein inhibitors. *Eur. Heart J.* 31, 149–164 (2010).

23 Boudík F, Reissigová J, Hrach K *et al.* Primary prevention of coronary artery disease among middle aged men in Prague: twenty-year follow-up results. *Atherosclerosis* 184(1), 86–93 (2006).

24 Stein EA, Stroes ES, Steiner G *et al.* Safety and tolerability of dalcetrapib. *Am. J. Cardiol.* 104, 82–91 (2009).

25 Stein EA, Roth EM, Rhyne JM, Burgess T, Kallend D, Robinson JG. Safety and tolerability of dalcetrapib (RO4607381/JTT-705): results from a 48-week trial. *Eur. Heart J.* 31, 480–488 (2010).

Websites

101 WHO. The top 10 causes of death. Fact sheet No 310. 2008. www.who.int/mediacentre/factsheets/fs310/en/index.html (Accessed 21 January 2011)

102 University of Oxford. REVEAL: Randomized Evaluation of the Effects of Anacetrapib Through Lipid-modification (NCT01252953), 1 December 2010. http://clinicaltrials.gov/ct2/show/01252953?term=reveal&rank=1 (Accessed 12 January 2011)

103 National Heart Lung and Blood Institute. AIM-HIGH: niacin plus statin to prevent vascular events (NCT00120289), 4 August 2010. http://clinicaltrials.gov/ct2/show/NCT00120289?term=aim-high&rank=3 (Accessed 12 January 2011)

104 University of Oxford. Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) NCT00461630, 19 July 2010. http://clinicaltrials.gov/ct2/show/NCT00461630?term=hps+thrive&rank=1 (Accessed 12 January 2011)

105 LaRoche. A Study of the Effect of R04607381 on Vascular Function in Patients with Coronary Heart Disease (CHD) or CHD-Risk Equivalent Patients (Dal-VESSEL) NCT00655538. http://clinicaltrials.gov/ct2/show/NCT00655538?term=00655538&rank=1 (Accessed 12 January 2011)

106 Hoffman-LaRoche. A Study of the Effect of R04607381 on Atherosclerotic Plaque in Patients with Coronary Artery Disease (Dal-PLAQUE) NCT00655473. http://clinicaltrials.gov/ct2/show/NCT00655473?term=dalcetrapib&rank=3 (Accessed 12 January 2011)

107 Hoffman-LaRoche. A Study of the Effect of Dalcetrapib on Atherosclerotic Disease in Patients with Coronary Artery Disease (Dal-PLQUE-2) NCT01059682. http://clinicaltrials.gov/ct2/show/NCT01059682?term=dalcetrapib&rank=1 (Accessed 12 January 2011)