Cholesteryl ester transfer protein inhibition and endothelial function: enough with the surrogates

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This editorial refers to ‘Vascular effects and safety of dalcetrapib in patients with or at risk of coronary heart disease: the dal-VESSEL randomized clinical trial†, by T.F. Lüscher et al., on page 857

Statins significantly reduce cardiovascular events in a broad category of patients at risk for or with established atherosclerotic cardiovascular disease; however, a substantial residual risk remains even when LDL-cholesterol (LDL-C) levels are lowered to 70 mg/dL.1 A part of this residual risk is related to low HDL-C levels.2 Epidemiological studies, the known favourable biological actions of HDL and its key constituents, as well as experimental studies have suggested beneficial athero-protective effects of HDL, making HDL a suitable therapeutic target.2 However, unlike LDL-C lowering, HDL-C-raising interventions with currently available agents, such as niacin, fibrates, or peroxisome proliferator-activated receptor γ agonists, have not been conclusively or consistently demonstrated to reduce cardiovascular events.3 In the last several years, inhibition of a key enzyme, CETP (cholesteryl ester transfer protein), involved in HDL metabolism, has become a focus of attention since CETP inhibition leads to increases in HDL-C levels.4 CETP is a glycoprotein, present in humans, rabbits, primates, and hamsters, but absent in rodents, dogs, horses, cows, and pigs, that facilitates transfer of cholesteryl ester from HDL particles to LDL/very low-density lipoprotein (VLDL) particles in exchange for triglycerides, thereby participating in reverse cholesterol transport and regulating circulating HDL-C levels.4 Recent observations have also highlighted the fact that CETP remodels HDL particles to generate pre-β-HDL particles that participate as initial acceptors of ABCA-1-mediated cholesteryl transfer from peripheral tissues.5 Despite the inverse relationship between CETP activity and HDL-C levels, epidemiological and genetic association studies have provided somewhat conflicting and inconsistent results with respect to the relationship between CETP activity and coronary heart disease (CHD) risk.6,7 Therefore, to date it remains uncertain whether CETP is a foe or a friend in atherosclerosis.

Torcetrapib, the first oral CETP inhibitor to advance to phase III clinical trials, unexpectedly increased cardiovascular and non-cardiovascular mortality (cancer and infection related) despite marked increases in HDL-C and additional reductions in LDL-C, leading to abandonment of torcetrapib as a viable drug candidate in 2006.8 Torcetrapib also failed to reduce carotid intima-media thickness and coronary plaque in several phase II clinical trials.9–10 The precise reasons for the failure of torcetrapib remain to be fully defined, but off-target (non-CETP-dependent) toxicity resulting from increases in blood pressure and endothelial dysfunction from increased vascular endothelin expression may have played a role.11,12 Torcetrapib was shown to elevate arterial blood pressure by a non-CETP-related mechanism, most probably by stimulating aldosterone synthesis by activating L-type calcium channels in adrenal cells.3 However, modest blood pressure elevation by torcetrapib is unlikely to have accounted for all of the adverse cardiac and non-cardiac complications of torcetrapib, and other speculations have included torcetrapib generating non-functional/dysfunctional HDL and producing adverse effects on innate immunity.13

Unlike torcetrapib, dalcetrapib is a weaker CETP antagonist that acts as a CETP modulator, inhibiting cholesterol ester transfer between HDL and LDL/VLDL without inhibiting CETP-mediated transfer of cholesteryl ester between HDL particles; the latter effect thus preserves the generation of pre-β-HDL particles that are believed to be important in initiating reverse cholesterol transport.5 Dalcetrapib has been shown to raise HDL-C by ~30%
without a significant effect on LDL-C.\textsuperscript{3} Dalcetrapib has no adverse effects on aldosterone pathway or arterial blood pressure.\textsuperscript{1} Experimental studies with dalcetrapib in rabbits have yielded mixed results, with favourable effects in rabbits with mild hyperlipidaemia and lack of favourable effects in rabbits with severe hyperlipidaemia.\textsuperscript{4}

The favourable vascular effects of HDL-C have been attributed to its ability to stimulate reverse cholesterol transport, antioxidant and anti-inflammatory actions, as well as favourable effects on various aspects of endothelial function.\textsuperscript{2} Recent studies have shown that HDL stimulates endothelial nitric oxide production, activates endothelial nitric oxide synthase (eNOS), and promotes endothelial repair through involvement of SR-B1, the sphingosine pathway, and other potential cellular effects.\textsuperscript{5}

Lüscher et al. have now reported the results of the dal-VESSEL trial, a randomized double blind placebo-controlled trial of dalcetrapib on brachial artery reactivity as an index of endothelial function.\textsuperscript{14} In this study, 476 patients with known CHD or CHD equivalent status, with baseline LDL-C <100 mg/dL (with statin or ezetimibe use) and HDL-C <50 mg/dL were randomized to placebo or dalcetrapib 600 mg/day, and the endothelium-dependent vasodilator response in the brachial artery was assessed by ultrasound following a 5 min occlusion. Compared with placebo, there was no significant change in brachial artery reactivity with dalcetrapib at 12 weeks (primary endpoint) or at 36 weeks (secondary endpoint). Furthermore, ambulatory blood pressure measurement showed no significant changes with dalcetrapib compared with placebo at 12 or 36 weeks. Dalcetrapib reduced CETP activity by \(\sim 50\)% increased HDL-C by \(\sim 30\)% and increased apolipoprotein A-1 levels by \(\sim 10\)%.

Dalcetrapib had no effect on LDL-C, plasma biomarkers of inflammation (except for a 17% increase in lipoprotein-associated phospholipase A\textsubscript{2}, probably due to an increase in HDL-C), coagulation, and oxidative stress. Overall the drug was well tolerated and there was no difference in the rate of pre-specified adjudicated adverse events between placebo and dalcetrapib. Subgroup analysis failed to show any favourable effect in various subsets of patients, especially those with reduced baseline HDL-C levels.\textsuperscript{14} The authors appropriately concluded that dalcetrapib did not have any adverse effects on endothelial function or arterial blood pressure, although a pessimist might have concluded that dalcetrapib failed to improve endothelial function in spite of a 30% increases in HDL-C levels. These results are somewhat disappointing in view of the well known favourable effects of HDL on endothelial function as measured by endothelium-dependent vasodilator response as well as other aspects of endothelial function.\textsuperscript{2} In contrast to the results from the dal-VESSEL trial, direct infusion of reconstituted HDL in human subjects with hypercholesterolaemia has been shown to improve endothelial function rapidly in conduit arteries and in the microcirculation.\textsuperscript{15,16}

The dal-VESSEL trial does not provide a mechanistic insight as to why dalcetrapib failed to improve endothelial function despite a significant increase in HDL-C levels. The study was well designed with appropriate patient selection, and the data analysis was performed at a core laboratory, making it unlikely that methodological issues could explain the findings.\textsuperscript{14} Similarly, inclusion of patients with baseline normal HDL-C levels may have made it difficult to show an improvement, but subgroup analysis in low HDL-C patients also failed to show any improvement in endothelial function.\textsuperscript{14} It is possible that the increase in HDL-C levels with dalcetrapib was not sufficient to improve endothelial function; in fact, human studies of reconstituted HDL infusion demonstrating improved endothelial function were associated with substantially greater increases in HDL-C levels: 69% in the study of Speiker et al.\textsuperscript{15} or 200% in the study by Bisoendial et al.\textsuperscript{16} It is also not unreasonable to speculate that CETP modulation by dalcetrapib generates HDL that is functionally inactive, at least as far as endothelial function is concerned, thus adding further fuel to the controversy about CETP as a legitimate therapeutic target for atherosclerosis.\textsuperscript{4} Functional heterogeneity of HDL is supported by recent studies showing that HDL from patients with coronary artery disease fails to improve endothelial function and repair due to failure to induce eNOS, lending support to the concept that under certain conditions HDL may lack key vascular protective effects.\textsuperscript{17} Lack of a decrease in high sensitive C-reactive protein in this study and in the studies involving other CETP inhibitors that result in even larger increases in HDL-C levels and additional reductions in LDL-C levels, such as torcetrapib and anacertapib,\textsuperscript{18} also raises concerns about the anti-inflammatory functionality of elevated HDL-C levels following CETP inhibition. Nevertheless, while the results of the dal-VESSEL trial are disappointing, it should be recognized that brachial artery reactivity is only a surrogate of vascular health, and interventions that improve it may not necessarily improve clinical outcomes, and similarly lack of improvement in brachial artery reactivity may not necessarily preclude clinical benefit. The recently reported somewhat favourable results of dalcetrapib on imaging evidence of atherosclerosis in the dal-PLAQUE trial provide a hint of encouragement.\textsuperscript{19} When all is said and done, despite negative (endothelial function, inflammatory markers) or marginally positive effects on surrogate endpoints (plaque), only large-scale event-based clinical trials can ultimately adjudicate whether CETP inhibition with specific inhibitors that do not share the off-targetotoxic effects of torcetrapib is going to be a therapeutic advance or another target gone wrong. Fortunately, a large randomized event-based clinical trial of dalcetrapib involving \(>15\,000\) post-acute coronary syndrome patients has completed recruitment (dal-OUTCOMES trial) and the results will become available in 2013. This study should provide a rather definitive answer as to whether CETP is a friend or foe in atherosclerosis. Similarly, a large outcomes trial of anacertapib, a potent CETP inhibitor which does not raise blood pressure but raises HDL-C by \(>100\)% and reduces LDL-C by \(>40\)% without reducing high sensitive C-reactive protein, is on its way and should provide additional results within the next 4–5 years (REVEAL trial; www.clinicaltrials.gov). Reliance on surrogate markers of vascular function and structure, while of interest, does not take into account other known or unknown biological vascular or non-vascular effects that ultimately influence net clinical outcomes. Enough with the surrogates; let us wait for outcomes please.

**Conflict of interest:** The author is a member of the steering committee of the dal-OUTCOMES trial.
References


