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REVIEW ARTICLE

CHOLESTERYL ESTER TRANSFER PROTEIN (CETP) INHIBITORS AND THEIR ROLE IN CARDIOVASCULAR DISORDERS

A. Kontush

National Institute for Health and Medical Research (INSERM), Dyslipidemia, Inflammation and Atherosclerosis Research Unit (UMR 939), Paris France; Université Pierre et Marie Curie-Paris 6, Paris, France; AP-HP, Groupe Hospitalier Pitié-Salpétrière, Paris, France

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SUMMARY

Low levels of high-density lipoprotein cholesterol (HDL-C) constitute a major independent cardiovascular risk factor. Novel strategies for raising HDL-C to address residual cardiovascular risk after statin treatment are required. Cholesteryl ester transfer protein (CETP) inhibitors are small molecules that interact with CETP and inhibit its capacity to facilitate heteroexchange of neutral lipids (cholesteryl esters and triglycerides) between HDL and apolipoprotein B (Apo B)-containing lipoproteins. CETP inhibitors are presently the most potent HDL-raising agents, with a dose-dependent HDL-C elevation of up to +150%. Based on these findings, three small-molecule inhibitors of CETP, torcetrapib, dalcetrapib (JTT-705) and anacetrapib (MK-0859), have been developed, which induce increases in circulating concentrations of HDL-C while decreasing those of low-density lipoprotein cholesterol (LDL-C) and Apo B. While the development of torcetrapib was abandoned as a result of excessive mortality in clinical trials, potentially reflecting its hypertensive effect related to elevated aldosterone levels, anacetrapib holds promise as the only drug belonging to this class that combines high potency with a good safety profile.

INTRODUCTION

Elevated levels of low-density lipoprotein cholesterol (LDL-C) are well established to represent a major cardiovascular (CV) risk factor. HMG-CoA reductase inhibitors (statins) effectively reduce LDL-C levels and concomitantly decrease CV risk by up to −40%; however, a substantial residual CV risk persists following statin treatment (1). Low levels of high-density lipoprotein cholesterol (HDL-C) constitute another major independent CV risk factor (2). Importantly, low HDL-C concentrations are associated with CV events even at very low levels (< 70 mg/dL) of LDL-C in patients treated with statins (3). Novel strategies for raising HDL-C to address residual CV risk after statin treatment are therefore required.

Therapeutic strategies to raise HDL-C levels may target several pathways, which primarily include the formation of HDL particles and their intravascular remodeling. Approaches that target HDL formation may involve stimulation of hepatic and/or intestinal production of apolipoprotein A-I (ApoA-I), the major protein component of HDL, as well as infusion of recombinant ApoA-I, reconstituted HDL, delipidated HDL or ApoA-I-mimetic peptides (4). Approaches targeting HDL remodeling are characterized by increased numbers of circulating HDL particles or by delayed catabolism of ApoA-I, which is maintained longer in the circulation as a result of enhanced formation of lipid-rich HDL. Mechanistic strategies to achieve these goals include inhibition of cholesteryl ester transfer protein (CETP) as a major approach (5) (Fig. 1).

CETP inhibitors are small molecules that interact with CETP and inhibit its capacity to facilitate heteroexchange of neutral lipids (cholesteryl esters and triglycerides) between HDL and Apo B-containing lipoproteins (6). CETP inhibitors are presently the most potent HDL-raising agents, with a dose-dependent HDL-C elevation of up to +150% (6). The therapeutic strategy to achieve HDL-C elevation via CETP inhibition derives from the plasma lipid profile associated with genetic CETP deficiency, which involves elevated HDL-C, often accompanied by decreased LDL-C levels, a combination that is typically antiatherogenic (7). Based on these findings, three small-molecule inhibitors of CETP, torcetrapib, dalcetrapib (JTT-705) and anacetrapib (MK-0859), have been developed, which induce an increase in circulating concentrations of HDL-C while decreasing those of LDL-C and Apo B (Table I). Other classes of pharmacological CETP inhibitors include 2,3-dihydro-3,8-diphenylbenzo[1,4]oxazines, tetrahydroquinoline A, 2-arylbenzoxazoles and benzylamino-methanones (8-11); none of these compounds has, however, yet entered large-scale clinical studies.

Correspondence: Dr. Anatol Kontush, INSERM Unit 939, Pavillon Benjamin Delessert, Hôpital de la Pitié, 83 Boulevard de l'Hôpital, 75651 Paris Cedex 13, France. E-mail: kontush@chups.jussieu.fr.

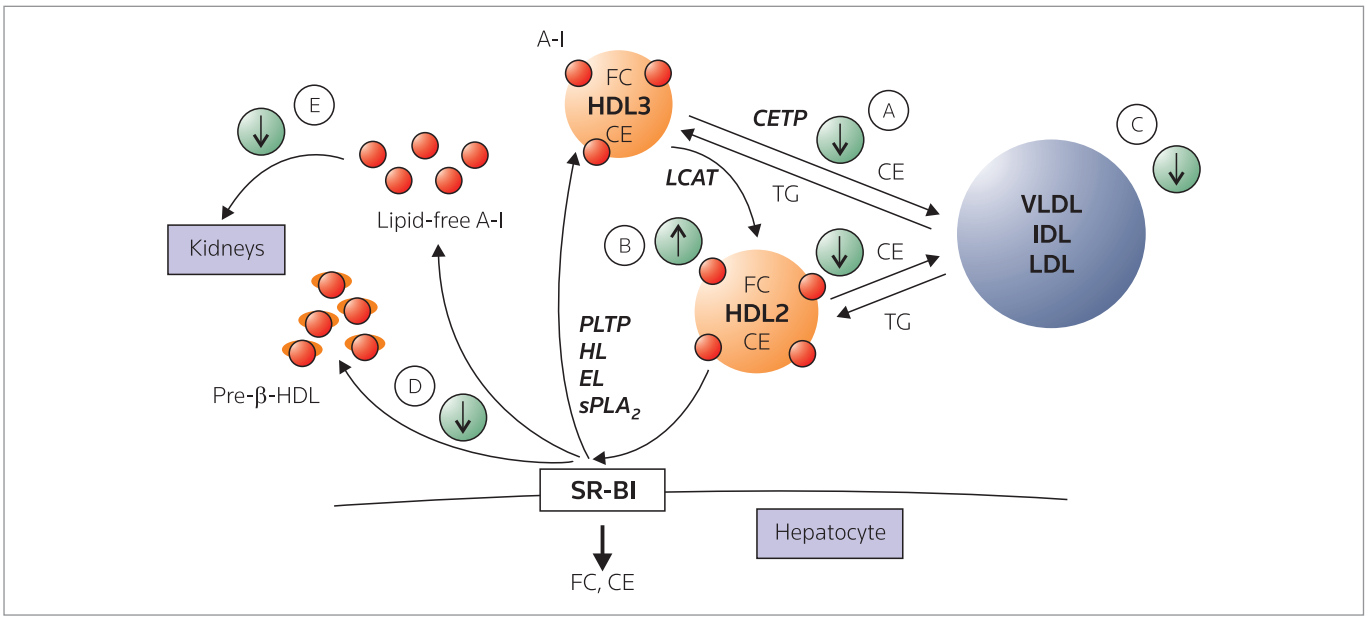


Figure 1. Major pathways underlying the action of cholesteryl ester transfer protein (CETP) inhibitors on plasma lipoprotein metabolism. (**A**) Decreased CETP activity resulting in diminished heteroexchange of cholesteryl ester and triglyceride between high-density lipoprotein (HDL) and triglyceride-rich lipoproteins; as a consequence, HDL is enriched in cholesteryl ester and depleted in triglyceride. (**B**) Preferential increase in circulating levels of large, light, cholesterol-rich HDL2. (**C**) Diminished levels of Apo B-containing lipoproteins. (**D**) Attenuated recycling of lipid-poor/lipid-free ApoA-I. (**E**) Delayed catabolism of ApoA-I. EL, endothelial lipase; HL, hepatic lipase; TG, triglyceride; CE, cholesteryl ester; FC, free cholesterol; PLTP, phospholipid transfer protein; LCAT, phosphatidylcholine-sterol acyltransferase (lecithin-cholesterol acyltransferase); VLDL, very-low-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein.

Table I. *Properties of CETP inhibitors.*

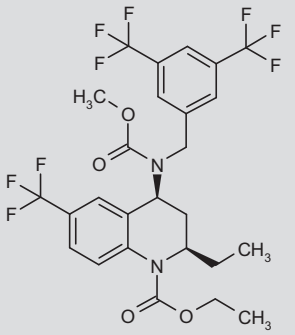
Agent	Potency	Effects on HDL	Effects on Apo B-containing lipoproteins	Off-target effects
Anacetrapib (MK-0859)	High	Increase in ApoA-I, Apo-E and HDL-C levels; preferential increase in large HDL	Decrease in LDL-C and Apo B levels	Unknown
Dalcetrapib (JTT-705)	Low	Increase in ApoA-I, Apo-E, HDL-C and HDL CE levels; preferential increase in large HDL	Decrease in LDL-C and TG levels	Unknown
Torcetrapib	High	Increase in ApoA-I, ApoA-II, Apo-E, HDL-C and HDL CE levels; decrease in HDL TG levels; preferential increase in large HDL	Decrease in LDL-C, TG and Apo B levels	Hypertensive effect related to elevated aldosterone levels; abandoned as a result of excessive mortality

CE, cholesteryl ester. TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

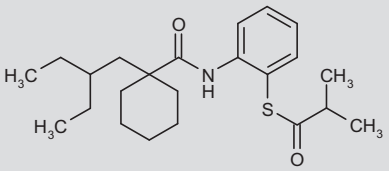
TORCETRAPIB

Torcetrapib, developed by Pfizer, became the first CETP inhibitor to enter clinical trials, which revealed marked efficacy for the drug in improving the atherogenic plasma lipid profile (Table I). Early studies demonstrated that torcetrapib dose-dependently inhibited CETP activity by –12% to –80% and increased HDL-C by +28% to +91% at doses of 30 and 240 mg/day, respectively, in healthy young normolipidemic subjects (12). In subjects with low HDL-C, treatment with torcetrapib at 120 and 240 mg/day raised plasma HDL-C concentrations by +46% and +106%, respectively (13). Importantly, CETP inhibition by torcetrapib led to a reduction in the triglyceride content of HDL particles and an increase in cholesteryl ester content (12). Consistent with these data, torcetrapib improved the abnormal composition of HDL2 and HDL3 particles in type IIB hyperlipidemia, increasing cholesteryl ester, phospholipid and ApoA-I and decreasing triglyceride content (14).

As a result, torcetrapib treatment strongly modified the heterogeneity of circulating HDL particles. Indeed, torcetrapib preferentially increased large, light HDL2-C (+87%) as compared to small, dense HDL3-C (+29%), resulting in elevated mean HDL particle size (Fig. 1). In addition, torcetrapib increased plasma levels of ApoA-I, raised the amount of ApoA-I in the alpha-1 HDL subpopulation, increased



Torcetrapib



Dalcetrapib

ApoA-I pool size and decreased the fractional catabolic rate of ApoA-I, thereby prolonging its residence time in the circulation. Such beneficial effects of torcetrapib on HDL metabolism may have resulted from normalization of ApoA-I lipidation subsequent to normalized cholesteryl ester/triglyceride ratio in the HDL lipid core (15). In a similar fashion, torcetrapib reduced the fractional catabolic rate of ApoA-II, thereby increasing its plasma levels (16).

Importantly, torcetrapib reduced plasma levels of Apo B-containing, triglyceride-rich lipoproteins (Fig. 1). Thus, circulating levels of ApoA-I and Apo-E were increased by +27% and +66%, respectively, while those of Apo B were reduced by –26% at a dose of 240 mg/day in healthy subjects (12). In non-atorvastatin-treated dyslipidemic patients, torcetrapib reduced levels of Apo B-containing lipoproteins primarily as a result of the enhanced clearance of very-low-density lipoprotein (VLDL)-associated Apo B-100, whereas clearance of LDL Apo B-100 was not significantly affected (17). In contrast, on a background of atorvastatin, the clearance of Apo B-containing lipoproteins was accelerated by torcetrapib as a result of upregulation of the LDL receptor (17). Indeed, VLDL enrichment in triglycerides resulting from CETP inhibition may potentiate lipolysis of these particles by lipoprotein lipase (LPL), thereby allowing their accelerated conversion to LDL and clearance from plasma.

DALCETRAPIB

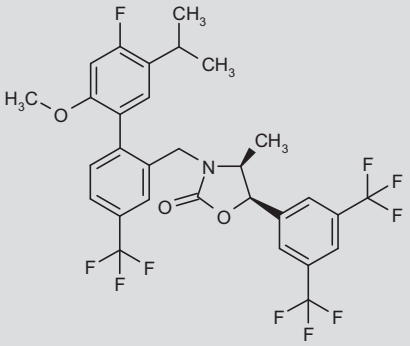
Another CETP inhibitor, **dalcetrapib** (JTT-705), developed by Japan Tobacco/Roche, is equally able to correct the atherogenic plasma lipid profile in dyslipidemic subjects (Table I). Indeed, dalcetrapib at a dose of 900 mg/day inhibited CETP by –37% and increased HDL-C by +34%, ApoA-I by +15%, HDL2 by +59% and HDL3 by +19% in subjects with mild hyperlipidemia (18); comparable effects were observed in patients with type II dyslipidemia (19) and familial hypoalphalipoproteinemia (20). In phase IIa trials, dalcetrapib at doses of 300, 600 and 900 mg for 4 weeks raised HDL-C by up to +36% at 900 mg/day in combination with a statin, and ApoA-I by up to +16% as monotherapy; in parallel, CETP activity was decreased by up to –38% (21). In a double-blind trial performed in subjects with coronary heart disease or coronary heart disease risk equivalents, CETP inhibition with dalcetrapib (900 mg/day) on a background of atorvastatin (10-80 mg/day) for 24 weeks increased HDL-C by +33.4%, decreased CETP activity by –53.5%, increased CETP mass by +80.8% and increased ApoA-I by +11.4% (22). In patients with type II hyperlipidemia, dalcetrapib (600 mg/day for 4 weeks) elevated plasma HDL-C by +26% and lowered triglyceride levels by –22% (23).

Dalcetrapib can also reduce concentrations of LDL-C, but only slightly and at a high dose, whereas levels of Apo B remain unaffected (19). Dalcetrapib is therefore a less potent CETP inhibitor compared to torcetrapib in the clinical setting; indeed, torcetrapib at 120 mg increased HDL-C substantially more than dalcetrapib at 900 mg (13).

ANACETRAPIB

Anacetrapib (MK-0859), a CETP inhibitor currently under development by Merck, is distinguished by its high potency in elevating HDL-C levels (Table I). Indeed, anacetrapib increases HDL-C to a greater extent (up to +129%) than other molecules in this class of drugs (24). Furthermore, anacetrapib potently reduced LDL-C up to –38% at the highest dose of 300 mg/day (24). In a double-blind, randomized, placebo-controlled phase I study performed in patients with dyslipidemia, anacetrapib at doses of 10, 40, 150 or 300 mg/day for 28 days produced dose-dependent lipid-altering actions, with maximal effects of +129% in HDL-C, +47% in ApoA-I, –38% in LDL-C and –26% in Apo B. To reach the plateau of the effects of plasma lipids in this study, the optimal dose of anacetrapib was 150 mg/day with a meal (24). Thus, anacetrapib exhibits a greater HDL-C elevation than torcetrapib or dalcetrapib, whereas the LDL-C reduction is similar to that provided by statins (24).

A subsequent study revealed that anacetrapib 10, 40, 150 and 300 mg once daily for 8 weeks produced mean percent changes from baseline to week 8 in LDL-C of –16%, –27%, –40% and –39%, respectively, and for HDL-C of +44%, +86%, +139% and +133%, respectively, in patients with primary hypercholesterolemia or mixed hyperlipidemia (25). In parallel, plasma Apo B levels were reduced by up to –30% and ApoA-I levels were elevated up to +47%. Importantly, anacetrapib, both as monotherapy and coadministered with atorvastatin, potently reduced plasma levels of lipoprotein(a) (Lp[a]) up to –50% (25). The net result of treatment with anace-



Anacetrapib

trapib on a background of atorvastatin amounted to more than doubling of HDL-C levels and –70% lowering of LDL-C.

Preliminary results recently obtained in the Determining the Efficacy and Tolerability of CETP Inhibition with Anacetrapib (DEFINE) trial showed that anacetrapib 100 mg/day increased HDL-C levels by +138.1% relative to placebo after 18 months in patients with coronary heart disease or at high risk for coronary heart disease (26). By 24 weeks, LDL-C levels were reduced by –39.8% versus placebo. Intriguingly, and in contrast to other CETP inhibitors, plasma levels of triglycerides were not significantly affected by anacetrapib treatment in published trials.

Importantly, torcetrapib, dalcetrapib and anacetrapib are chemically distinct and differ considerably in their mechanisms of interaction with CETP. First, torcetrapib and anacetrapib inhibit CETP-mediated lipid transfer with similar potencies, while dalcetrapib is a less potent inhibitor (27). In addition, inhibition of CETP by both torcetrapib and anacetrapib is not time-dependent, whereas the potency of dalcetrapib significantly increases with time (27), consistent with S–S bond formation with a Cys13 residue in CETP (28, 29). Furthermore, anacetrapib binds to CETP reversibly, whereas torcetrapib forms a nonproductive complex with HDL. In addition, anacetrapib, torcetrapib and dalcetrapib compete with one another for binding to CETP; the binding site of dalcetrapib is, however, different from that occupied by torcetrapib (30). Finally, each CETP inhibitor induces tight binding of CETP to HDL, indicating that the inhibition of CETP activity by these small molecules requires the formation of a complex between CETP and HDL (27).

CLINICAL TRIALS

The first large-scale, prospective, placebo-controlled interventional trial assessing the impact of a CETP inhibitor on CV risk, the Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) trial, was prematurely terminated in December 2006 as a consequence of excess mortality in the treatment group (torcetrapib 60 mg/day) relative to placebo (31). In this study, more than 15,000 patients at high risk for CV disease were randomized to either torcetrapib or placebo on a background of atorvastatin for a median of 550 days. Despite highly favorable changes in the lipid profile in the torcetrapib arm (HDL-C elevation +72%; LDL-C reduction –25%), CV mortality increased by +40%, the rate of CV events by +25% and non-CV death by +100% (31). Furthermore, mean common carotid intima–media thickness progression was higher in subjects with familial hypercholesterolemia and mixed dyslipidemia receiving torcetrapib plus atorvastatin than in subjects receiving atorvastatin alone in the Rating Atherosclerotic Disease change by Imaging With A New CETP Inhibitor (RADIANCE) 1 and 2 studies (32). These data suggested adverse effects of CETP inhibition per se and provoked serious criticism of this therapeutic approach (33).

In the ILLUMINATE trial, torcetrapib treatment was, however, associated with a significant increase in aldosterone levels, with changes in serum electrolyte levels indicative of mineralocorticoid excess, and with elevation of blood pressure (+5.4 mmHg in systolic blood pressure) (31). Given that every 10 mmHg increase in systolic blood pressure is associated with approximately a +25% increase in CV risk, such a hypertensive effect of torcetrapib might have negated potential benefits of HDL-C elevation (34). These findings suggest an off-target mechanism of torcetrapib toxicity unrelated to increase in HDL-C and involving activation of mineralocorticoid receptors by aldosterone, with subsequent induction of hypertension (35) (Table I). Data from the RADIANCE 1 and 2 studies support mineralocorticoid-mediated, renin- and angiotensin-independent off-target toxicity in patients receiving torcetrapib as a contributing factor to an adverse outcome (32). Consistent with this conclusion, hypertensive effects for torcetrapib and CP-532623, a closely related CETP inhibitor, were observed in monkeys and human subjects (36).

In contrast to torcetrapib, dalcetrapib and anacetrapib do not increase blood pressure in humans, an observation which discounts a class effect directly related to CETP inhibition, which might result in altered steroid metabolism through enhanced delivery of HDL-derived cholesterol to the adrenals (37). Indeed, anacetrapib did not increase blood pressure in dyslipidemic subjects, suggesting that potent CETP inhibition by itself does not increase blood pressure (24). Similarly, anacetrapib did not affect levels of aldosterone, sodium, potassium, bicarbonate and C-reactive protein (CRP). The incidence of adverse events was similar for placebo and all anacetrapib treatment groups in this study; there were no increases in systolic or diastolic blood pressure in any treatment arm (25). Furthermore, no changes were noted in blood pressure, electrolyte or aldosterone levels with anacetrapib (100 mg/day) compared to placebo through 76 weeks in patients with coronary heart disease or at high risk for coronary heart disease in the DEFINE trial (26). Prespecified adjudicated CV events occurred in 16 patients treated with anacetrapib (2.0%) and in 21 patients on placebo (2.6%) ($P = 0.40$). The prespecified Bayesian analysis indicated that this event distribution provided a predictive probability (confidence) of 94% that anacetrapib would not be associated with a 25% increase in CV events, as seen with torcetrapib (26, 31).

Similarly, the incidence of adverse events was low on dalcetrapib treatment (300 and 600 mg) and did not differ between the dalcetrapib and placebo arms (21). Furthermore, CV adverse events were similar across treatment groups, with no clinically relevant changes in blood pressure or electrocardiographic findings. Dalcetrapib showed no clinically relevant differences versus placebo

in adverse events (except an increased frequency of diarrhea and headache), laboratory parameters, including aldosterone, electrolytes and electrocardiograms, and vital signs, including blood pressure. A small (+0.05%) but significant (P = 0.008) increase in CRP was, however, observed on dalcetrapib treatment (22).

The absence of a class effect for CETP inhibitors on aldosterone metabolism and blood pressure is further supported by data obtained in animal models, which reveal that torcetrapib induces an acute increase in blood pressure in all species evaluated (38); in parallel, plasma levels of aldosterone and corticosterone are elevated. Significantly, no blood pressure increase is observed with anacetrapib (38). In vitro, torcetrapib induces aldosterone release from adrenocortical cells (38) and enhances aldosterone production and cytochrome P450 11B2 mRNA levels (21). In contrast, increased adrenal steroid levels are not observed with anacetrapib. These results further distinguish anacetrapib as a potent CETP inhibitor that possesses a good safety profile.

Another argument against the role of CETP in the hypertensive effect of torcetrapib is derived from the mechanism of activation of the renin–angiotensin–aldosterone system, which involves mineralocorticoid and blood pressure responsiveness to dietary salt intake and is not related to plasma CETP levels in humans (39). Consistent with these data, CETP deficiency is not associated with hypertension in man (34, 40).

Imaging studies designed to evaluate the impact of torcetrapib on coronary atheroma with intravascular ultrasound in the Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation (ILLUSTRATE) trial revealed that the progression of coronary atherosclerosis was not altered by the treatment (41, 42). Interestingly, increasing levels of HDL-C in torcetrapib-treated patients in this trial were associated with fewer CV events and a beneficial impact on plaque progression (31, 43); in a multivariable analysis, changes in HDL-C levels independently predicted the effect on atherosclerosis progression (44). In contrast, HDL-C elevation was not associated with carotid intima–media thickness change in the RADIANCE 1 and 2 studies (32).

Epidemiological data on the relationship between cardiovascular risk and CETP activity can shed more light on the role of this protein in the development of atherosclerotic disease; such data are, however, controversial. Thus, plasma CETP activity is negatively related to coronary risk in studies of three common CETP genotypes (TaqIB, I405V and 629C>A) (45-48). In parallel, however, HDL-C levels are elevated and triglyceride levels are reduced in subjects with low CETP activity in these studies, suggesting potential confounding between HDL-C and triglycerides. Furthermore, baseline CETP levels are associated with future coronary artery disease in a subset of hypertriglyceridemic subjects from an apparently healthy population (49). In addition, baseline CETP levels are positively correlated with carotid intima–media thickness measured prospectively in patients with familial hypercholesterolemia treated with statins (50).

However, low CETP activity was associated with elevated cardiovascular risk in a prospective investigation of participants of the Framingham Heart Study (51), which is inconsistent with the above data. Similarly, low plasma concentrations of CETP were associated with elevated cardiovascular and all-cause mortality in the Ludwigshafen Risk and Cardiovascular Health (LURIC) study (52). Finally, increasing on-statin CETP mass was inversely related to coronary outcomes in the Pravastatin or Atorvastatin Evaluation and Infection Therapy - Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) cohort, particularly among subjects with low LDL-C levels (53). When analyzing these results, one should keep in mind that an adverse plasma lipid profile is associated with elevated plasma CETP activity rather than mass, and that changes in CETP mass often do not parallel those in endogenous CETP activity (6).

Results of animal studies tend to support a beneficial action for CETP inhibitors on atherosclerosis. Thus, dalcetrapib given to cholesterol-fed rabbits at a mean dose of 255 mg/kg daily caused a +90% increase in HDL-C levels and a –70% decrease in atherosclerotic lesion area in the aortic arch after 6 months of treatment (54). Consistent with these data, torcetrapib increased HDL-C by +207% and inhibited aortic atherosclerosis by –60% in rabbits fed an atherogenic diet (55). Interestingly, atheroprotective effects of CETP inhibition can also be observed in cholesterol-fed rabbits when CETP activity is reduced by intravenous injection with antisense oligodeoxynucleotides against CETP targeted to the liver (56). Similarly, immunization with a CETP-derived peptide elevated plasma HDL-C and reduced atherosclerosis in New Zealand white rabbits (57).

EFFECTS ON REVERSE CHOLESTEROL TRANSPORT AND OTHER ASPECTS OF HDL FUNCTIONALITY

HDL particles possess key atheroprotective functions, including the capacity to efflux cellular cholesterol, as well as antiinflammatory, antioxidative, antiapoptotic, cytoprotective, antiinfective and antithrombotic activities (5). The effects of lipid-modifying drugs on HDL functionality therefore require particular attention when evaluating their clinical efficacy.

The potent capacity of HDL to promote cellular cholesterol efflux is typically reflected in accelerated reverse cholesterol transport (RCT) from peripheral tissues to the liver for excretion through the bile. Robust HDL-C elevation provided by CETP inhibitors may therefore be expected to enhance RCT and hence inhibit atherogenesis. CETP inhibitors do not, however, alter fecal excretion of cholesterol in human subjects (15, 58). HDL-derived cholesteryl ester can be delivered to the liver either directly from HDL through selective uptake by scavenger receptor class B type I (SR-BI) in a process termed direct RCT, or indirectly via CETP-mediated transfer to Apo B-containing lipoproteins followed by lipoprotein uptake by the hepatic LDL receptor (indirect RCT) (35). In man, the CETP-mediated transfer of cholesteryl ester from HDL to Apo B-containing lipoproteins represents a quantitatively significant route for the return of cholesterol from peripheral tissues to the liver; LDL particles constitute the major cholesteryl ester acceptor among Apo B-containing lipoproteins in normolipidemic, normotriglyceridemic humans (59).

Indirect cholesterol flux from HDL to the liver mediated by Apo B-containing lipoproteins appears to be attenuated rather than accelerated under CETP inhibition. Thus, torcetrapib induces only partial CETP inhibition, indicating that a residual cholesteryl ester transfer from HDL to Apo B-containing lipoproteins is maintained. Such cholesteryl ester transfer is, however, limited, as reflected by the reduction in cholesteryl ester content of VLDL and LDL particles (60). However, reduc-

tion in cholesterol flux through the indirect pathway may be compensated by acceleration of such flux through HDL. In support of this possibility, torcetrapib treatment generates large Apo E- and cholesteryl ester-rich HDL particles, which efficiently promote cholesterol efflux from macrophages through the ATP-binding cassette sub-family G member 1 (*ABCG1*)-dependent pathway (61). Furthermore, treatment with anacetrapib 300 mg/day for 8 weeks increased HDL-C by approximately twofold and improved cellular cholesterol efflux mediated by HDL (62). In addition, as large HDLs can efficiently efflux cellular cholesterol via the *ABCG1* and scavenger receptor class B member 1 (SR-BI) pathways (63), such cholesterol efflux may be enhanced following CETP inhibition (14). Consistent with these data, HDL particles generated in rabbits treated with dalcetrapib at a dose of 300 mg/kg are fully functional in terms of their capacity to efflux cholesterol from macrophages (64).

Moreover, partial inhibition of CETP by torcetrapib normalizes ApoA-I levels within large, alpha-migrating HDL and increases plasma concentrations of HDL ApoA-I by delaying ApoA-I catabolism (15). Large ApoA-I-containing HDLs represent ideal ligands for the selective uptake of cholesteryl ester by SR-BI (65); CETP inhibition may therefore enhance the capacity of HDL particles to deliver cholesteryl ester to the liver, thereby allowing efficient hepatic return of cholesteryl ester via the direct route of RCT (14).

Whereas the capacity of HDL to efflux and transport cholesterol does not appear to be compromised by CETP inhibitors, little is known about other atheroprotective activities of HDL. Intriguingly, the excess of non-CV deaths observed in the torcetrapib group in the ILLUMINATE trial was primarily derived from cancer (24 vs. 14 in the placebo group) and infection (9 vs. 0) (31). These adverse effects appear to be specific to torcetrapib, as a meta-analysis of randomized, controlled trials revealed that increase in HDL-C per se is not associated with higher non-CV death (66). Therefore, deleterious effects of torcetrapib on biological activities of HDL particles other than cholesterol efflux cannot be excluded. Indeed, in addition to producing hypertension and baseline vasoconstriction, torcetrapib markedly inhibits acetylcholine-induced vasodilation in rabbit arteries and impairs endothelial function in vivo independent of CETP inhibition and HDL-C elevation. This deleterious effect may have contributed to increased CV risk in patients treated with torcetrapib in clinical trials (67). Other adverse effects of CETP inhibition may include decreased nitric oxide production by endothelial cells secondary to reduced stimulation of endothelial nitric oxide synthase by very large HDL, diminished recycling of atheroprotective small, lipid-poor HDL (68) (Fig. 1), increased ApoA-I oxidation secondary to its prolonged plasma residence time and elevated secretion of endothelin-1 secondary to enhanced HDL-C levels (69). In contrast, direct effects of torcetrapib on lipopolysaccharide inactivation (70) or macrophage inflammatory response (62) can be excluded according to recent studies. Moreover, recent data suggest that CETP inhibitors possess potential for the improvement of some aspects of HDL functionality, acting by enriching HDL in cholesteryl ester and correcting core lipid composition of HDL particles (5, 71, 72).

CONCLUSIONS

The ultimate answer regarding the clinical utility of CETP inhibitors, including anacetrapib and dalcetrapib, will be provided by ongoing multicenter, randomized, double-blind, placebo-controlled clinical trials, such as the DEFINE study evaluating anacetrapib 100 mg/day in patients with coronary heart disease or at high risk for coronary heart disease (73), or the Randomized, Double-blind, Placebo-controlled Study Assessing the Effect of RO4607381 on CV Mortality and Morbidity in Clinically Stable Patients With a Recent Acute Coronary Syndrome (Dal-OUTCOMES) study assessing the effect of dalcetrapib 600 mg/day on CV events and mortality in patients with recent acute coronary syndrome (74). The Dalcetrapib HDL Evaluation, Atherosclerosis and Reverse Cholesterol Transport (Dal-HEART) program also includes three surrogate endpoint trials, which will provide further information as to the contribution of CETP to CV disease (75). Presently available data indicate that the concept of CETP inhibition remains a viable strategy to reduce residual CV risk persisting following statin treatment. Anacetrapib holds promise as the only drug belonging to this class that combines high potency with a good safety profile.

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