Cholesteryl Ester Transfer Protein (CETP) Inhibition Beyond Raising High-Density Lipoprotein Cholesterol Levels
Pathways by Which Modulation of CETP Activity May Alter Atherogenesis

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Abstract—Raising high-density lipoprotein cholesterol (HDL-C) is a promising strategy in the struggle to prevent cardiovascular disease, and cholesteryl ester transfer protein (CETP) inhibitors have been developed to accomplish this. The first results are encouraging, and, in fact, in rabbits, inhibition of CETP reduces atherosclerosis. Because human data regarding the reduction of atheroma burden require more time, the biochemical mechanisms underlying the putative atheroprotection of CETP inhibitors are currently dissected, and several pathways have emerged. First, CETP inhibition increases HDL-C and reduces low-density lipoprotein cholesterol (LDL-C) levels consistent with CETP lipid transfer activity and its role in reverse cholesterol transport (RCT). This coincides with putative beneficial increases in both HDL and LDL size. However, many aspects regarding the impact of CETP inhibition on the RCT pathway remain elusive, in particular whether the first step concerning cholesterol efflux from peripheral tissues to HDL is influenced. Moreover, the relevance of scavenger receptor BI and consequently the central role of HDL in human RCT is still unclear. Second, CETP inhibition was shown recently to increase antioxidant enzymes associated with HDL, in turn associated with decreased oxidation of LDL. Atheroprotection in man is currently anticipated based on the improvement of these biochemical parameters known to influence atherosclerosis, but final confirmation regarding the impact of CETP inhibition on cardiovascular outcome will have to come from trials evaluating clinical end points. (Arterioscler Thromb Vasc Biol. 2006;26:000-000.)

Key Words: atherosclerosis ■ CETP inhibitor ■ lipid metabolism ■ HDL

Inhibition of cholesteryl ester transfer protein (CETP) holds promise as a novel approach to prevent coronary artery disease (CAD) because of its profound effect on high-density lipoprotein cholesterol (HDL-C) levels. The scope of this review is to discuss the impact of CETP inhibition beyond this primary effect.

The physiological function of CETP in the circulation, that is, transfer of neutral lipids (cholesteryl esters [CEs] and triglycerides [TGs]) between lipoproteins, and the causes and effects of natural variation in CETP activity, has been the subject of many reviews on CETP and CETP inhibition.1–6 Therefore, we have chosen to summarize the current understanding of lipoprotein remodeling by CETP (Figure, 1 and 2). Importantly, in dyslipidemias characterized by increased concentrations of TG-rich particles (mainly very low-density lipoprotein [VLDL] and VLDL remnants), the CE transfer from HDL shifts from LDL toward VLDL, particularly large VLDL1 (Figure, 2).7,8 This is considered to be atherogenic because CE-enriched VLDLs become substrates for hepatic lipase (HL), resulting in the generation of deleterious small dense LDL.9 Recently, increased CETP activity was indeed associated with increased risk for CAD in subjects with elevated TGs.10 Taking this together, it could be hypothesized that in hypertriglyceridemic individuals, CETP inhibition may be antiatherogenic by reducing small dense LDL formation.

Recent data on CETP inhibition in rabbits and humans show that pharmacological inhibition of CETP has similar effects on the lipid profile as naturally occurring CETP deficiency.11 Notably, next to the marked increases in HDL-C and HDL size, the CETP inhibitor torcetrapib induced a significant increase in LDL size, caused by both an increase in large LDL particles and a decrease in small LDL particles, suggesting a less atherogenic lipid profile.12 Recently, similar effects were reported for JTT-705.13 In this review, we focus on how changes in lipoprotein concentrations and lipoprotein neutral lipid content after CETP inhibition may influence cholesterol exchange processes between the periphery, the
circulation, and the liver, thereby covering the reverse cholesterol transport (RCT) pathway. We furthermore discuss the effects of CETP inhibition on fecal sterol excretion. Finally, we briefly touch on the effects of CETP inhibition on the anti-inflammatory and antioxidative properties of HDL.

**CETP Inhibition and RCT**

RCT is generally invoked to provide the rationale for the antiatherogenic properties of HDL. It concerns the removal of excess cholesterol from peripheral tissues for elimination by the liver and secretion into bile (Figure). Many of its players have been identified, and their particular functions are confirmed by in vitro and animal studies. The Figure, 1, illustrates the most direct route for removal of cholesterol in humans; the ATP-binding cassette transporter A1 (ABCA1) shuttles cholesterol from peripheral cells to lipid-poor apolipoprotein A-I (apoA-I). Next, lecithin:cholesterol acyltransferase (LCAT) esterifies free cholesterol, and the resulting CEs induce maturation of HDL particles. These HDLs can deliver cholesterol to the liver via the scavenger receptor BI. CETP transfers CEs from HDL to apoB lipoproteins (VLDL) in exchange for TG. CETP inhibition results in accumulation of CE-rich HDL and decreases LDL-CE. Normally, CE-rich LDL is taken up by the liver via the LDL receptor, and TG in TG-rich HDL is hydrolyzed by HL, resulting in regeneration of lipid-poor apoA-I. CETP inhibition increases HDL2 fraction and may also increase lipid-poor apoA-I. The total impact of CETP inhibition on cholesterol efflux is unclear.
Cholesterol Efflux From Peripheral Tissues to HDL

One of the atheroprotective properties of HDL is its ability to act as an acceptor of cholesterol from peripheral cells, or specifically macrophage foam cells in the arterial wall. This initial step in RCT depends mainly on the presence of cholesterol transporters in the cell membrane and the presence and avidity of extracellular acceptor particles, mostly thought to be HDL. CETP has been suggested to affect this process by changing the cholesterol efflux capacity of donor and acceptor cells and by modulating the uptake capacity as well as availability of initial acceptor particles (Figure 3).

Cholesterol Donor Capacity of Cells

A role for CETP in the cellular cholesterol donor capacity was proposed after it was shown that CETP is expressed by monocyte-derived macrophages present in fatty streaks and atherosclerotic plaques of human origin. Zhang et al also reported that blood-borne macrophages of a CETP-deficient subject were less efficient in cholesterol efflux compared with a control subject, and that COS-7 cells transiently overexpressing CETP showed an increased efflux capacity to medium, whereas influx capacity was unaltered. In contrast to this potentially antiatherogenic role for CETP in macrophages, suppression of CETP synthesis in a liver cell line (HepG2) enhanced cholesterol efflux to HDL, whereas this was unaltered in an adipose tissue cell line (SW872). Considering the crucial role of macrophage foam cells in atherogenesis, further research into the exact function of CETP produced by these cells is warranted.

Cholesterol Acceptor Capacity of HDL Particles

By changing the neutral lipid composition and size of HDL, CETP may affect the avidity of these particles for cholesterol. In CETP-deficient individuals and after CETP inhibition, average HDL size increases, and the cholesterol content of mainly large HDL particles is increased. Indeed, it was reported that plasma from homozygotes for CETP null defects had a reduced acceptor capacity for cholesterol from lipid-laden macrophages. These investigators concluded that the large CE-rich HDL particles in CETP deficiency are defective as cholesterol acceptors. These effects can be understood today when considering that ABCA1 only mediates cholesterol and phospholipid (PL) efflux to lipid-free or lipid-poor apoA-I. In CETP deficient mice (SR-BI) as shown in mice. In humans and rabbits, the presence of CETP in the circulation creates a major diversion from this route. In exchange for TGs, CETP facilitates transfer of CE from HDL to apoB-containing particles, which can also be taken up via the LDL receptor. Ultimately, excess liver cholesterol can be excreted as neutral sterols and bile acids into bile for removal via the feces. Although this model is widely accepted, it is of note that there exists very little experimental evidence that HDL is indeed central to this dynamic process in humans. Nevertheless, RCT provides an excellent tool to discuss the effects of CETP inhibition on HDL metabolism, and we review the role of CETP in each step of this pathway.

Availability of Cholesterol Acceptor Particles

It was postulated that the driving force of cellular cholesterol efflux is not the concentration of the initial acceptors (lipid-poor apoA-I or HDL) but the presence of secondary acceptors (LDL and VLDL) and proteins and enzymes, such as LCAT, CETP, and lipases (PLTP, HL, LPL), which redistribute cholesterol from these acceptor particles to the HDL particles. CETP inhibition. Interestingly, it has been shown that in...
patients with low HDL-C, torcetrapib decreased the fractional catabolic rate of apoA-I, whereas the synthetic rate was unaltered.\textsuperscript{26} This illustrates that the extrapolation of data from animals to man, even if these animals possess endogenous CETP, is challenging.

Together, it is difficult to establish the role of CETP in the important initial step in the RCT pathway, which in vivo occurs within the confinement of the arterial wall. Here, we depend on artificial systems in which only 1 factor that contributes to cholesterol efflux can be assessed at once. For example, SR-BI–mediated efflux is usually addressed in the rat hepatoma cell line Fu5AH, whereas for ABCA1 expression, fibroblasts or cAMP-stimulated macrophages are generally used.\textsuperscript{15} There is accumulating evidence that both cholesterol efflux pathways work complementarily, and respond diverely to, for example, the PL content of acceptor particles or metabolic changes.\textsuperscript{36,48,49} Moreover, because the relative contributions of ABCA1, SR-BI (and human homologue CLA-1),\textsuperscript{30,51} ABCG1, and ABCG4 in macrophage efflux are not firmly established in human physiology,\textsuperscript{17} we wish to refrain from predicting to what extent CETP inhibition will affect the initial step in the RCT pathway.

**Uptake and Storage of Cholesterol in Adipose Tissue**

Adipose tissue is an important storage and sensing organ for cholesterol homeostasis, and the metabolic consequences of adiposity play a role in the progression of atherosclerosis.\textsuperscript{52,53} Moreover, both adipocytes and adipose tissue–derived macrophages secrete inflammatory proteins that may contribute to the development of a systemic inflammatory state.\textsuperscript{54} Therefore, it is of interest to underline that in addition to the liver, adipose tissue is the second major site of CETP production.\textsuperscript{55} Maybe the adipocyte may quickly regulate plasma CETP levels in response to physiological changes.\textsuperscript{56}

Indeed, CETP gene expression in adipose tissue is significantly upregulated by dietary cholesterol as observed in hamster and human adipose tissue.\textsuperscript{51,55} There are indications that CETP plays a role in the selective uptake of HDL CE in adipose tissue, which could accommodate removal of cholesterol from the circulation.\textsuperscript{56,57} Vassiliou and McPherson showed in vitro that extracellular CETP (mimicking CETP in the circulation) accounts for 14% of CE-selective uptake in adipose tissue independent of the presence of apoB receptors and SR-BI. These authors propose that this so-called lateral cholesterol transport and storage may be antiatherogenic, and that CETP inhibitors may influence this process. This was addressed recently in liver cells, as is discussed below.\textsuperscript{59}

CETP may also play a role in intracellular cholesterol homeostasis; Izem and Morton showed that suppression of CETP synthesis in the adipose tissue cell line 3T3-L1 causes CE accumulation.\textsuperscript{21} CETP activity is moreover positively correlated with BMI and waist-to-hip ratio, but it is unclear whether this is cause or consequence.\textsuperscript{60,61} Interestingly, a significant weight gain was observed in rabbits receiving JTT-705 in combination with a severe hypercholesterolemic diet for 3 months compared with controls on the same diet.\textsuperscript{62} However, this was not observed in a previous study on a milder hypercholesterolemic diet.\textsuperscript{63}

Given this information, it could be inferred that inhibition of CETP gives rise to a reduction in lipid uptake in adipose tissue, but whether this will have an impact on cholesterol homeostasis, systemic inflammatory status, and atherosclerosis is unclear. Therefore, it would be of interest to study the effect of CETP inhibition on adipose tissue, inflammatory markers, and body weight changes.

**Uptake of Cholesterol by the Liver**

In mice, which lack CETP, \textasciitilde70% of circulating CE is taken up directly from HDL by the liver,\textsuperscript{64} which is mediated by SR-BI.\textsuperscript{65} Similar data have been obtained in the hamster, a low-CETP animal.\textsuperscript{66} As soon as higher CETP levels come into play, the delivery route of CEs to the liver changes dramatically. In rabbits, 70% of CEs are transferred from HDL to apoB-containing particles and subsequently taken up in the liver by the LDL receptor and related receptors and only 30% via apoA-I–containing particles.\textsuperscript{67} In humans, a recent kinetic analysis by Schwartz et al indicates that irreversible CE output from lipoproteins to the liver comes from apoB-containing particles and not from HDL.\textsuperscript{68} This would suggest that HDL-mediated cholesterol uptake in the liver does not play an important role in humans. This could mean that CETP inhibition will affect the normal uptake of CEs in the human liver via the LDL pathway. Therefore, we discuss the effects of CETP on both HDL and LDL receptor–mediated pathways as illustrated in the Figure, 4.

**SR-BI/CLA-1**

CLA-1, the human homologue of SR-BI, is expressed mainly in adrenal tissues, liver, and reproductive organs and was shown to have receptor affinity for all lipoproteins, including native HDL, LDL, and VLDL, but also modified oxidized LDL (oxLDL) and acetylated LDL.\textsuperscript{69,70} However, the data on the relationship between HDL remodeling by CETP and cholesterol uptake by SR-BI are contradicting. Kinoshita et al observed that in SR-BI–overexpressing CHO cells, the uptake of CE per HDL particle is increased from CE-rich HDL of CETP-deficient individuals compared with normal HDL.\textsuperscript{71} This suggests that SR-BI may efficiently take up cholesterol from CE-enriched HDL after loss of CETP function. In contrast, CETP enhances CE uptake in the liver of mice overexpressing human LCAT or apoA-I,\textsuperscript{72,73} leading to less atherosclerosis in hgt LCAT/CETP mice.\textsuperscript{72} Moreover, the enhanced liver uptake was directly from HDL and not attributable to transfer to apoB-containing particles.\textsuperscript{73} Because the role of CLA-1 in humans is not established, the implications of CETP inhibition for this cholesterol uptake route in the liver cannot be properly discussed.

**LDL Receptor**

As already indicated, the main route for delivery of CE to the liver in humans is thought to be mediated by apoB-containing lipoproteins. Remarkably, increased apoB catabolism has been observed in homozygous CETP deficient subjects compared with unaffected controls.\textsuperscript{74} This is consistent with upregulation of the LDL receptor in rabbits injected with antisense CETP oligonucleotides\textsuperscript{75} and downregulation of the LDL receptor in mice that overexpress human CETP.\textsuperscript{76} It has
been suggested that upregulation of the LDL receptor in homozgyous CETP deficiency is a compensatory mechanism to counteract reduced affinity for the LDL receptor of the observed polydisperse apoB-containing particles.77 Depending on the CETP inhibitor, marked or modest reductions in LDL-C have been shown in humans. A similar effect was also observed when CETP inhibitors were used in combination with statins.12,26,27 Whether this is also attributable to an upregulation of the LDL receptor remains to be determined. Alternatively, the reduced LDL-C levels after CETP inhibition can also be explained by the decreased CETP-mediated transfer of CE from HDL to LDL. In this case, CE are not removed from the circulation via LDL, and the influx into the liver may in fact be reduced. In this respect, it is interesting to note that after CETP inhibitor treatment, LDL size increases, particularly by a decrease in small LDL, which may suggest that the remaining LDL particles are less atherogenic.12,13

As an alternative pathway, the uptake of CE by the liver could also be mediated via apoE-containing HDL because CETP inhibition is associated with increased apoE levels.25,27,78 It has been shown that apoE-containing HDL particles can be taken up by the members of the LDL receptor family79–81 but also by SR-BI.82,83 Furthermore, Yamashita et al showed that apoE-rich HDL from CETP-deficient individuals had a higher affinity for LDL receptors on fibroblasts than LDL itself.84 Although Clark et al did not confirm that the increase of apoE levels can be accounted for by an apoE-enrichment of HDL, it can be hypothesized that CETP inhibitors may lead to enhanced removal of CE via apoE-containing HDL particles.25,78

**Receptor-Independent Selective Uptake of HDL-CE**

In 1987, Granot et al reported that addition of CETP to liver cells (HepG2) in vitro enhanced selective uptake of HDL-CE.85 Later, this was attributed to the indirect effect of CETP-mediated transfer of HDL-CE to other lipoproteins before uptake because this presupposed that selective uptake of HDL-CE could be blocked by antibodies against the LDL receptor and other apoB and apoE receptors.80 In contrast, Gauthier et al recently observed that exogenous CETP enhanced the uptake of HDL-CE in mouse hepatocytes of both LDL receptor 0-mice and SR-BI−/− mice in vitro.86 Torcetrapib partially inhibited this selective uptake mediated by endogenous CETP in these experiments. In vivo, in adenoviral CETP-expressing mice, high doses of intravenously injected torcetrapib attenuated CETP-mediated decrease in total cholesterol only partially. The authors suggest that the remaining decrease in total cholesterol was attributable to hepatic cholesterol clearance by cell-associated CETP, and that this antiatherogenic function of CETP may not be inhibited by torcetrapib. Nevertheless, the overall importance in humans needs to be established because kinetic analysis by Schwartz suggests that selective uptake of HDL-CE in man plays a minor role in total hepatic uptake of CE.88

In summary, CETP inhibition is likely to influence the hepatic uptake of CE from the circulation via apoE-rich HDL, maybe in combination with upregulation of the LDL receptor.

**Secretion of Cholesterol by the Liver Into the Intestine**

The ultimate step in the removal of cholesterol from the body is the excretion of neutral sterols and bile acids in the feces, which can be upregulated in humans by the infusion of apoA-I or reconstituted HDL (rHDL).57,88 These studies support the idea that HDL is central to the removal of (peripheral) cholesterol in humans, and it was hypothesized that increasing HDL-C and apoA-I levels by CETP inhibition may also increase fecal cholesterol excretion. However, Brousseau et al did not observe a difference in fecal sterol excretion, even after torcetrapib induced a 100% to 125% increase in HDL-C in patients with low HDL-C at baseline.26 Similarly, in rabbits, attenuation of CETP activity by red pepper was shown to slightly increase TG excretion but did not affect cholesterol excretion.89 In htg CETP mice, it has also been observed that liver cholesterol levels and cholesterol synthesis are strongly affected by infusion of rHDL, but this had no effect on fecal excretion.90 A lack of change in fecal cholesterol secretion was also observed in ABCA1 knockout mice that have almost no HDL-C in the circulation.91 Together, these data suggest that the earlier steps in the RCT pathway (ie, the enrichment of HDL with CE), and, consequently, the increase of HDL-C, have little to do with the removal of cholesterol from the human body as a final step in RCT. On the other hand, it could be that fecal sterol excretion does not accurately reflect changes in hepatic cholesterol influx after CETP inhibition. This hypothesis is supported by the observation that rats metabolize CE taken up via HDL CE more efficiently into bile acids than CE from LDL.92,93 Finally, it may be that torcetrapib did not induce fecal sterol excretion to the same extent as a large intravenous dose of apoA-I, but there may have been a reduction in fecal sterol excretion, which was too small to detect. Although there is no evidence that CETP inhibition stimulates fecal cholesterol excretion, overexpression of human CETP in mice has been shown to enhance fecal cholesterol excretion.94 This effect could be related to the increased CE content of the liver of these mice, but these investigators also observed a small increase in the expression of ABCG5. Because this transporter is known to affect hepatic sterol excretion, this suggests that CETP can affect cholesterol output in this model, albeit not along the classical route of RCT.94

In summary, these CETP inhibition data support the view that HDL may not represent the major vehicle to deliver CE to the liver for subsequent elimination in bile in humans. There is no consensus regarding the significance of this final excretion step with respect to maintaining whole body flux in RCT, neither whether this final step in RCT is actually connected to and reflects what is assumed the most important step for the atherosclerosis process (ie, cholesterol efflux from macrophages).95,96 This leaves the question whether CETP inhibition may affect atherogenesis by altering RCT as yet unanswered.

**CETP Inhibition and Anti-Inflammatory and Antioxidative Properties of HDL**

It has been long recognized that apart from its role in RCT, HDL possesses properties that may reduce atherosclerosis by...
attenuating inflammation of the vascular wall and by preventing oxidation of LDL. For details, we refer to a recent review by Barter. It was recently shown that rHDL can effectively block neutrophil infiltration in the carotid artery of the rabbit, an early event of inflammation of the vessel wall. Other investigators reported that apoA-I can inhibit T-cell activation of macrophages, which, in turn, will reduce the production of inflammatory cytokines and chemokines. In addition, through prevention of LDL oxidation, a key event in atherosclerosis, HDL has also been shown to inhibit the formation of foam cells. Most of this effect is currently attributed to enzymes that are associated with HDL metabolism. CETP inhibition are scarce. Elevation of PON1 activity was observed, and plasma CETP levels, suggesting that CETP is protective under these physiological conditions.

Impact of CETP Inhibition on Atherogenesis and Concluding Remarks

The purpose of CETP inhibition therapy is to protect against CAD by reducing atherosclerosis or stabilizing vulnerable plaques. Awaiting the first human data, studies with rabbits have provided a basis for optimism. Already in 1998, Sugano et al observed markedly reduced atherosclerosis in Japanese white (JW) rabbits on a high-cholesterol diet (0.3%) using an antisense strategy that inhibits CETP expression. Furthermore, 3 different vaccines that induce antibodies against CETP have been shown to reduce atherosclerosis in New Zealand white (NZW) rabbits on a cholesterol-rich diet. Pharmacological inhibition with JTT-705 prevented atherosclerosis progression in JW rabbits on a 0.2% cholesterol diet. However, no significant effects were observed in a different study in JW rabbits that received a similar dose of JTT-705, but were on a 0.25% cholesterol diet. This may be explained by more severe diet-induced hypercholesterolemia in the latter rabbits, but the treatment period was also shorter. More recently, pharmacological inhibition of CETP with torcetrapib also prevented atherosclerosis in NZW rabbits on a 0.2% cholesterol/10% coconut oil diet.

It is a major challenge to determine what mechanisms are primarily responsible for the atheroprotective effect of CETP inhibition. Of course the marked increase in HDL-C levels is put forward; but which functions of HDL are responsible for atheroprotection? Moreover, as illustrated in this review, CETP does not only affect HDL metabolism but also LDL metabolism. To protect the arterial wall against atherosclerosis, the following processes are thought important: (1) preventing inflammation, and internalization/modification of LDL to attenuate foam cell formation; (2) stimulating cholesterol efflux from lipid-laden macrophages; and (3) enhancing LDL uptake by the liver, thereby limiting LDL modification and plasma residence time of this atherogenic lipoprotein. The current literature provides evidence that CETP inhibition may affect each of these processes. At the same time, this review shows that many aspects regarding the functions of CETP in human metabolism and the importance of human RCT are still elusive. The first issue that remains to be resolved is the role of CETP in adipose tissue. Second, with respect to the classical concept of RCT, there is concern that CETP inhibition reduces the flux of cholesterol through RCT both by decreased recycling of HDL acceptor particles and by diminished hepatic cholesterol uptake via the LDL receptor. The unchanged fecal cholesterol excretion after CETP inhibition may be considered an indication of this; however, it can also indicate that HDL is not central to liver cholesterol uptake in man. Importantly, this does not rule out that HDL serves as an initial acceptor of cholesterol from lipid-laden macrophages in the intima. There remains a strong need to determine what parameter can give us in vivo information on this crucial first step of RCT, rather than waiting for changes in arterial wall morphology or atheroma burden. Furthermore, it is not clear what the relative contri-
bution of RCT to human atheroprotection is, especially when compared with the anti-inflammatory and antioxidant properties of HDL. Finally, this review has addressed the complex biology of CETP in RCT, but it remains to be seen whether this is relevant when it comes to atheroprotection.

Despite all the uncertainties, the impact of CETP inhibition on raising HDL-C and decreasing both LDL-C and small dense LDL illustrates its potential to reduce atherosclerosis in man. Moreover, CETP inhibition may protect against atherosclerosis by improving the anti-inflammatory and antioxidant actions of HDL, as demonstrated previously in rabbits and now for the first time in man. These data suggest that CETP inhibition goes beyond raising HDL-C levels alone.

Acknowledgments

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References


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