High-density lipoprotein (HDL) possesses antiatherogenic properties that include reverse cholesterol transport (RCT), maintenance of endothelial function, and protection against thrombosis.1,2 The concentration of HDL largely determined by the cholesteryl ester transfer protein (CETP) that decreases the ratio of HDL-cholesterol (HDL-C) over low-density lipoprotein-cholesterol (LDL-C). In this review, we will discuss the rationale and effectiveness of using HDL as a therapeutic target, by reducing CETP activity, as a means of cardiovascular morbidity reduction.

The Role of HDL in Atherosclerosis

Metabolism and Pathophysiology

HDL has been proposed to have several antiatherogenic properties that include the ability to mediate cholesterol efflux from macrophages, antioxidant capacity, and inflammatory properties, nitric oxide–promoting activity,1,2 and the ability to transport proteins with their own intrinsic biological activities.3 The steps describing the removal of excess cholesterol from macrophages to ultimate disposition in the feces are collectively known as RCT and are schematically summarized in Figure.4 Small nascent HDL particles composed of phospholipids and apolipoproteins (apo) are synthesized mainly in the liver and the intestine. These particles obtain additional apolipoproteins, free and esterified cholesterol, and excess phospholipids from chylomicrons and very LDL (VLDL) during their lipolytic conversion into triglyceride-depleted remnants. Free cholesterol is also acquired from peripheral tissues. HDL-associated apolipoproteins, including apoAI, play a central role in this process, serving as a signal transduction protein to mobilize cholesteryl esters (CEs) from intracellular pools. Of similar importance are ATP-binding cassette transporters A1 and ATP-binding cassette transporters G1 proteins expressed on the macrophage cell surface that mediate the transfer of cellular unesterified cholesterol to nascent discoloidal and maturing globular HDL.5 The accepted cholesterol in HDL is subsequently transferred into CE by lecithin cholesterol acyl transferase, an enzyme that is also activated primarily by apoAI. Subsequently, HDL can transport its CE back to the liver via interaction with the scavenger receptor BI on hepatocytes that selectively delipidates HDL, delivering CE to hepatocytes, and releasing CE-depleted particles back into the circulation, therefore reinitiating another round of RCT.6 In humans, there is a second indirect RCT pathway involving CETP, which is probably more relevant. CETP exchanges triglyceride from chylomicrons, VLDL, and their remnants for CE from HDL. As a result, CE that is transferred to these apoB-containing particles can be taken up by the liver via receptors, including the LDL receptor and LDL receptor–related protein.7 At the same time, HDL is enriched with triglyceride, which renders it a good substrate for catabolism by hepatic lipase, reducing the plasma concentration of HDL.8

Epidemiological Data Associating HDL and Coronary Artery Disease

Despite early observations suggesting an inverse relationship among HDL-C levels and coronary artery disease (CAD),9 the possible protective role of HDL in atherogenesis received little attention until its rediscovery by Miller and Miller in 197510 and the confirmatory results from a series of large studies (Honolulu, Framingham, and Tromsö heart studies).11–13 In the Framingham Study, the risk for CAD was shown to increase sharply as HDL-C levels fell progressively <40 mg/dL (1.04 mmol/L). Published later, the Quebec Cardiovascular Study, also demonstrated a 13% increase in the risk of CAD for every 10% reduction in HDL-C.14 In a large meta-analysis of >300 000 people and during 2.79 million population years of follow-up, Di Angelantonio et al15 confirm the protective and prognostic importance of HDL.

The potential protective effect of HDL against atherosclerosis had long been suggested by observations in human populations, where HDL-C concentrations higher than 75 mg/dL (1.9 mmol/L) were associated with prolonged life (longevity syndromes) and relative freedom from CAD.16 The publication of the Helsinki Heart Study in 1987,17 in which a simultaneous 11% increase in HDL and reduction in LDL-C levels during gemfibrozil therapy were accompanied by a 34% reduction in myocardial infarction rates, raised the issue of whether efforts

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to increase HDL-C levels should be undertaken in patients with normal or slightly elevated total cholesterol levels.

Concerns that the association of low HDL-C with increased CAD risk is merely a marker of hypertriglyceridemia and elevated remnant particle concentrations were initially rejected by the Prospective Cardiovascular Münster Study, demonstrating that the increased risk associated with low HDL-C was independent of serum triglyceride levels. \(^{18}\)

However, a more recent study showed that elevated triglyceride levels do associate with increased risk for myocardial infarction, ischemic heart disease, and death. \(^{19}\)

Taken together with the observation that genetically reduced levels of HDL-C associate with decreased rather than increased risk of ischemic heart disease, and death, \(^{19}\)

HDL as a Therapeutic Target

The National Cholesterol Education Program defines an HDL-C level <40 mg/dL (1.04 mmol/L) as a categorical risk factor for CAD. \(^{25}\)

Despite this, treating patients for low HDL-C can be quite challenging for a number of reasons. Firstly, raising HDL requires significant lifestyle modifications (smoking cessation, weight loss, aerobic exercise, and moderate alcohol consumption) and often the use of additional medications (nicotinic acid and fibrates) that are not always free of side effects. Secondly, because most of the available pharmacological interventions also affect other lipoproteins, including LDL, it is not exactly clear whether a raise in HDL-C per se reduces morbidity and mortality.

Finally, although European and American guidelines clearly set goals for LDL-C and non–HDL-C based on global cardiovascular risk evaluation, similar targets for HDL-C are yet to be defined.

The development of selective CETP inhibitors during the past decade aimed to selectively raise HDL-C levels and augment its functionality. CETP catalyzes a hetero-exchange of CE in HDL for triglyceride in apoB-containing lipoproteins, including VLDL and chylomicrons. Although this is part of the indirect RCT pathway mentioned before, CETP-mediated hepatic cholesterol retrieval is not perfectly efficient,
especially under hyperlipidemic conditions (inefficient [V]) LDL uptake from plasma). Consequently, CE-rich lipoproteins can potentially remain in blood and drive atherogenesis. Moreover, the more HDL becomes enriched with triglyceride, the better substrate it becomes for hepatic lipase–mediated catabolism, thereby lowering HDL-C levels. The physiopathological rationale behind CETP inhibition, therefore, is that it preserves HDL, increases the plasma levels of HDL-C, and reduces the levels of atherogenic-proene lipoproteins.

The Development of Specific CETP Inhibitors

Relation Between CETP and Atherosclerosis: Lessons From Animals

Because CETP contributes to RCT (antiatherogenic) as well as induces a disadvantaged lipoprotein profile (proatherogenic), the role of CETP in atherosclerosis has been evaluated in mice that are naturally deficient for CETP. CETP expression is clearly proatherogenic in hyperlipidemic mouse models that accumulate VLDL remnants caused by attenuated receptor-mediated remnant clearance.26,27 However, CETP expression in these mouse models not only reduces HDL-C but also concomitantly increases VLDL-C.26 In fact, a recent study showed that CETP aggravates atherosclerosis by increasing VLDL-C rather than by decreasing HDL-C.28 These data thus indicate that CETP inhibition may be effective in reducing atherosclerosis, albeit the mechanism of action may largely depend on reduction of apoB-containing lipoproteins rather than on increasing HDL-C.

The effect of CETP on atherosclerosis development has also been evaluated in rabbits that naturally express CETP. Reduction of CETP activity by either vaccination against CETP29 or antisense oligodeoxynucleotides against CETP30 increased HDL-C and reduced plaque formation.26,30 Although it is tempting to assume that the HDL-C–raising effect caused the reduction in atherosclerosis, it should be noted that, also in rabbits, the reduction in CETP expression led to a reduction in LDL-C that may well have contributed to the antiatherogenic effect.

Interestingly, CETP has been suggested to be at the heart of the action of the HDL-C–raising effect of lipid-agents, such as statins, fibrates, and niacin.31 Indeed, we have shown that the lipid-lowering effects of atorvastatin,32 fenofibrate,33 and niacin34 in APOE*3-Leiden mice were accompanied by a concomitant increasing effect on HDL-C but only when these mice also express CETP. Interestingly, a recent study evaluating the effect of niacin on atherosclerosis in these mice, without and with concomitant treatment with simvastatin, showed a potent antiatherogenic effect of niacin, which was largely explained by the lipid-lowering effect of niacin (P.C.N. Rensen and J.W. Jukema, unpublished data, 2012).

Collectively, these animal studies indicate that reduction of plasma CETP concentration and activity in general reduces atherosclerosis development in mice and rabbits. However, because CETP reduction concomitantly increases HDL-C and decreases VLDL-C, it is hard to determine the relative contributions of these effects to the attenuation of atherosclerosis.

Atherosclerosis in CETP-Deficient Human Subjects

Indications in humans that CETP inhibition could be beneficial in terms of CAD prevention arose from studies in populations with loss-of-function polymorphisms in the CETP gene (located in 16q21). Subjects with reduced CETP activity and hyperalphalipoproteinemia seemed to be relatively protected from CAD and were long-lived.35 However, further reports of such CETP activity-loss mutations revealed a more complex picture. In another Japanese population, where a CETP gene polymorphism was associated with protein deficiency and marked elevations of HDL-C and apoA1,36 researchers found a statistically significant U-shaped relationship between HDL-C levels and the incidence of ischemic heart disease, with the incidence increasing proportionally for HDL-C levels >70 mg/dL (1.81 mmol/L). A pathophysiological explanation to this observation could be that in patients homozygous for loss of CETP activity polymorphisms, HDL particles become so saturated with CE they that practically become functionally inactive as cholesterol receptors. With the CETP pathway inactive, RCT would be completely dependent from the direct route of uptake by the liver through scavenger receptor BI. Ultimately their capacity for RCT would be compromised, thereby resulting in increased risk for CAD.

Subsequent large epidemiological studies were also confusing. In a large meta-analysis of 92 studies, from 1970 to 2008, including almost 114 000 participants, it was shown that moderate reductions of CETP mass and function were associated with modest (4.5%) elevation in HDL-C and a 5% reduction in the risk of cardiovascular events.37 Likewise, in a genome-wide analysis performed on 18 245 women enrolled in the Women’s Genome Health Study, a single-nucleotide polymorphism associated with loss of CETP activity was correlated with a rise in HDL of 3.1 mg/dL per allele and a correspondent 24% reduction in risk of myocardial infarction,38 whereas in a recently published meta-analysis of Mendelian randomization studies, single-nucleotide polymorphisms associated with

Table. Comparison of the Characteristics of the 4 CETP Inhibitors That Have Been and Are Currently Being Tested in Large Randomized Clinical Trials

<table>
<thead>
<tr>
<th>CETP Inhibitor</th>
<th>Effect on HDL-C</th>
<th>Effect on LDL-C</th>
<th>Off-Target Effects</th>
<th>Randomized Clinical Trial (Number of Patients Included)</th>
<th>Year of Publication (or Expected Completion Date)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Torcetrapib</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>ILLUMINATE (15 067)</td>
<td>2007</td>
</tr>
<tr>
<td>Dalcetrapib</td>
<td>+</td>
<td>None</td>
<td>+</td>
<td>DAL-OUTCOMES (15 871)</td>
<td>2012</td>
</tr>
<tr>
<td>Anacetrapib</td>
<td>+++</td>
<td>++</td>
<td>Not documented</td>
<td>REVEAL (aiming 30 000)</td>
<td>2017</td>
</tr>
<tr>
<td>Evacetrapib</td>
<td>+++</td>
<td>++</td>
<td>Not documented</td>
<td>ACCELERATE (aiming 11 000)</td>
<td>2015</td>
</tr>
</tbody>
</table>

ACCELERATE indicates Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition With Evacetrapib in Patients at a High-Risk for Vascular Outcomes; ILLUMINATE, Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events; DAL-OUTCOMES, Effect of Dalcetrapib on Cardiovascular Mortality and Morbidity in Clinically Stable Patients With a Recent Acute Coronary Syndrome; and REVEAL, randomized evaluation of the effects of anacetrapib through lipid.
reduced CETP activity were related to a 4% reduction in the risk of myocardial infarction.24 Quite confusingly, the Copenhagen City Heart Study initially demonstrated an increased risk for CAD, despite higher serum HDL-C in women with a loss-of-function CETP polymorphism, and a 36% lower risk for CAD in women with low HDL-C in the context of gain-of-function mutations.20 findings that were questioned by a more recent study of the same population, reporting opposite results when multiple alleles were affected, with genetic CETP inhibition associated with reduction in risk of CAD and risk of ischemic cerebrovascular disease along with a antiatherogenetic lipid profile and increased longevity.39 In a 10-year follow-up analysis of CAD patients treated with statins from the Regression Growth Evaluation Statin study, it was shown that a polymorphism associated with reduced CETP activity and increased HDL-C was actually associated with an increased all-cause and coronary mortality of 30% for the heterozygotes and 53% for the homozygotes.40 Finally, data derived from the Framingham Heart study also suggest an inverse relationship among the CETP activity and risk of CAD.41

These discrepancies among the different studies are difficult to explain. They could be attributed to the presence of confounding risk factors, concomitant (lipid-modifying) medication, the presence of other mutations involved in lipoproteins metabolism, etc. It is true, however, that no conclusions can be drawn on the optimal levels of CETP mass and activity that would warrant a reduction in the cardiovascular risk profile.

Clinical Trials: Use of CETP Inhibitors in Humans

Torcetrapib

Torcetrapib acts by increasing the affinity of CETP for HDL, thereby generating a tight complex that reduces the amount of CETP available to promote transfer of CE and triglyceride between lipoproteins.42 A daily dose of 60 mg torcetrapib induces a 60% decrease of HDL-C and 20% additional decrease of LDL-C levels. Nevertheless, imaging studies using intravascular ultrasound or B-mode ultrasound failed to provide evidence of regression in coronary atheroma burden or carotid intima media thickness.43-45

The Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events (ILLUMINATE) trial was a large randomized multicenter double-blind study conducted in 15 067 patients with known cardiovascular disease or diabetes mellitus, designed to test the hypothesis that CETP inhibition with torcetrapib would reduce the risk of subsequent cardiovascular events. Despite an observed 72% increase in HDL-C and a 25% decrease in LDL-C in the group receiving torcetrapib, the study was prematurely terminated because of a statistically significant excess of major cardiovascular events and deaths in the active treatment group.46 The most likely explanation was that a number of off-target effects of torcetrapib were responsible for these findings. Torcetrapib was associated with an increase in systolic blood pressure and serum aldosterone, a reduction in serum potassium, and an increase in serum concentrations of bicarbonate.46 Studies in animal models confirmed these findings, with torcetrapib inducing a proinflammatory profile,47 an acute increase in blood pressure, and an acute increase in plasma adrenal steroids that seems dependent on the presence of intact adrenal glands.48 Moreover, torcetrapib likely impairs endothelial function in a process that seems irrelevant to CETP inhibition per se or HDL-C levels.49

Despite the negative outcome of ILLUMINATE, torcetrapib was also associated with a number of encouraging findings on the potential role of CETP inhibitors. A post hoc analysis of the ILLUMINATE study revealed that coronary death and major cardiovascular events were lower in those patients with the higher increase of HDL-C and apoAI.46 Furthermore, the level of HDL-C achieved seemed to be actually an inverse predictor of events.50 Although this kind of analysis does not provide solid conclusions, it is still indicative that induced enhanced levels of HDL-C may have a beneficial effect.

As far as skepticism about the functional properties of CETP-treated HDL particles is concerned, in an in vitro study, HDL isolated from torcetrapib-treated patients was found to have either a normal or an enhanced ability to promote efflux of cholesterol from macrophages.51 In another study, using intravascular ultrasound data from a subset of the ILLUMINATE trial patients, torcetrapib-treated patients with the highest raise in HDL-C had a significant reduction in the coronary atheroma volume compared with the patients with the lower HDL-C values,52 suggesting that HDL in CETP-treated patients retains in vivo its properties and its capacity to promote cholesterol efflux from the tissues.

Dalcetrapib

Dalcetrapib was the first CETP molecule to be tested on animal models, where it successfully inhibited atherosclerosis in cholesterol-fed rabbits.52 In terms of mechanism of action, it is the least potent among the CETP inhibitors, binding to a unique site on CETP and inducing a conformational change of the enzyme that does not impair the formation of CETP-induced pre-β HDL, therefore, potentially preserving RCT.54 In comparison with other CETP inhibitors, a 600-mg daily dose of dalcetrapib (in patients already treated with a statin) induces a moderate decrease of CETP activity with an increase of HDL-C by 28% without affecting the levels of LDL-C.55 What accounts for the observed differences in LDL-C—lowering capacity among the different CETP inhibitors is not entirely clear.

After the unfavorable outcomes of the ILLUMINATE study, the effects of dalcetrapib on hemodynamics and the renin–angiotensin–aldosterone system were extensively investigated.56 In contrast to torcetrapib, dalcetrapib did not seem to increase blood pressure or renin–angiotensin–aldosterone-related gene expression, providing evidence that some of the known off-target effects of torcetrapib are not a generic characteristic of all CETP inhibitors. The effects of dalcetrapib and torcetrapib on aldosterone synthesis were also compared in tissue cultures of a human adrenocarcinoma cell line. Again, in contrast to torcetrapib, dalcetrapib had no effect on either aldosterone synthase or aldosterone production in these cells.77,78

Effect of Dalcetrapib on Progression or Regression of Atherosclerotic Plaque in Patients With Coronary Heart Disease (CHD) Including Patients With Other CHD Risk Factors (DAL-PLAQUE) and Safety, Tolerability and Effect on Endothelial Function, as Measured by Flow Mediated Dilatation, of Dalcetrapib in Patients With Coronary Heart Disease (CHD) or CHD Risk Equivalents (DAL-VESSEL) were 2 small
multicenter randomized studies to assess the potential effect of dalcetrapib treatment on atherosclerosis and endothelial function, respectively. Despite the lack of effect as far as the primary outcome measures were concerned, no safety issues arose either. This opened the way to Effect of Dalcetrapib on Cardiovascular Mortality and Morbidity in Clinically Stable Patients With a Recent Acute Coronary Syndrome (DAL-OCCUMES), a large phase III, randomized, multicenter, placebo-controlled clinical trial designed to test the hypothesis that CETP inhibition with dalcetrapib reduces cardiovascular morbidity and mortality in patients with recent acute coronary syndrome. The study was prematurely stopped in May 2012 on the basis of futility, whereas a second large randomized trial (DAL-OCCUMES 2) scheduled to investigate the effects of CETP inhibition in stable CAD was cancelled.

We should underline that the trial was not terminated because of safety issues. It is noteworthy, however, and despite the reassuring findings of the preliminary studies, that also in the case of dalcetrapib, a slight but statistically significant rise of 0.6 mm Hg of the blood pressure was observed and a small rise in CRP, questioning our reassurance that the torcetrapib off-target effects are not a class effect characteristic (albeit with significant heterogeneity in effect size) after all.

Anacetrapib
Anacetrapib is a far more potent CETP inhibitor compared with dalcetrapib. A daily dose of 100 mg has been shown to increase HDL-C concentration as much as 100% and lower LDL-C by 30% to 40% on top of statin therapy. Compared with torcetrapib, no effect on blood pressure, aldosterone, or serum electrolytes in humans has been observed, and anacetrapib does not stimulate the synthesis of aldosterone in adrenal cortical cells growing in tissue culture. Moreover, HDL isolated from people taking anacetrapib has a normal or enhanced functionality on its ability to promote efflux of cholesterol from macrophages, as assessed ex vivo.

After the encouraging results of the Determining the Efficacy and Tolerability of CETP Inhibition With Anacetrapib (DEFINE) study (a 18-month-long randomized trial aiming to assess the tolerability and efficacy of anacetrapib in patients with CAD or CAD risk equivalent disease), which demonstrated a favorable effect on LDL-C and HDL-C levels along with the absence of serious adverse effects, a large randomized multicenter clinical trial is currently on its way. The Randomized Evaluation of the Effects of Anacetrapib through Lipid-modification (NCT01252953) aims to determine whether lipid modification with anacetrapib (100 mg daily) reduces the risk of major coronary events (coronary death, myocardial infarction, or coronary revascularization) in patients with circulatory problems who have their LDL-C level treated with a statin. It is a large study aiming to randomize 30000 men and women with a history of myocardial infarction, cerebrovascular disease, peripheral arterial disease, or diabetes mellitus with other evidence of symptomatic CAD and will not be concluded before 2017.

Evacetrapib
Evacetrapib is another potent and selective CETP inhibitor that also seems to lack the off-target side effects of torcetrapib and possibly also of dalcetrapib. In a phase II, 12-week-long, randomized, placebo-controlled trial, where evacetrapib was given as a monotherapy or in combination with statins in 398 patients with dyslipidemia, it seemed (both as a monotherapy and in combination with statins) to significantly increase HDL-C and reduce LDL-C levels without any adverse effects being observed. As in the case of anacetrapib, a large phase III, randomized, multicenter, placebo control trial is currently on its way (Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition With Evacetrapib in Patients at a High-Risk for Vascular Outcomes (ACCELERATE), NCT01687998), aiming to evaluate the efficacy and safety of evacetrapib in patients at high risk for cardiovascular disease (previous acute coronary syndrome, documented cerebrovascular disease, peripheral arterial disease, or diabetes mellitus with documented CAD). This study is estimated to enroll 11000 patients for a follow-up period of 4 years, with the primary end point being cardiovascular death, myocardial infarction, stroke, coronary revascularization, or hospitalization with unstable angina.

An overview comparison of the 4 CETP inhibitors is provided in Table.

Conclusion
We would say that the role of CETP inhibition and HDL raising in the reduction of cardiovascular risk remains largely controversial. Despite the substantial body of evidence of an inverse relationship between levels of HDL-C and cardiovascular risk, low HDL-C levels have not been established as causative of this relationship or with the development of atherosclerosis. In fact, assessment of HDL functionality may be more relevant, given emerging experimental evidence of the pleiotropic potentially atheroprotective functions of HDL, independent of the HDL-C level. In the recent European Society of Cardiology/European Atherosclerosis Society guidelines on dyslipidemia management, HDL-C is recognized as a strong cardiovascular risk factor and recommended for use in risk estimation. However, given the lack of supportive evidence from clinical intervention trials to date, the guidelines do not recommend HDL-C as a treatment target.

Although the negative results of the ILLUMINATE and DAL-OCCUMES studies have definitely been discouraging, we are not convinced that CETP inhibitors should be abandoned altogether. The newer agents currently tested presumably do not have the safety issues of torcetrapib and are far more potent inhibitors of CETP, thus inducing higher levels of HDL-C while reducing the levels of LDL-C, properties that dalcetrapib lacked. The question of whether these pharmacological properties will prove clinically effective remains yet to be answered.

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**Key Words:** atherosclerosis • high-density lipoprotein • lipids and lipidprotein metabolism
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Ioannis Karalis, Patrick C.N. Rensen and J. Wouter Jukema

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