Mulling over the odds of CETP inhibition

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This editorial refers to ‘Safety and tolerability of dalcetrapib (RO4607381/JTT-705): results from a 48-week trial’, by E.A. Stein et al. on page 480

Both elevated plasma concentrations of LDL cholesterol and low concentrations of HDL cholesterol are important risk factors of coronary heart disease. In randomized controlled trials of >100 000 individuals, lowering of LDL cholesterol with statins was found to be safe and effective in reducing cardiovascular morbidity and mortality by 20–40%. As the flip side of the coin, 60–80% of cardiovascular events are not prevented by statin treatment. Therefore, and because low HDL cholesterol explains some of the residual risk of patients with well controlled LDL cholesterol levels, both lower treatment goals for LDL cholesterol (<70 mg/dL/1.75 mmol/L) and elevation of HDL cholesterol above at least 40 mg/dL (>1.05 mmol/L) are propagated. The clinical validity of this concept is currently evaluated in ongoing randomized clinical endpoint trials of statin combination therapies with ezetimibe, fenofibrate, nicotinic acid, or the cholesteryl ester transfer protein (CETP) inhibitor dalcetrapib.

CETP exchanges cholesteryl esters of HDL with triglycerides of apolipoprotein B (apoB)-containing lipoproteins (Figure 1). This has two important consequences in lipoprotein metabolism. First, notably large HDL2 particles lose their cholesteryl esters which have accumulated there as the result of efflux of phospholipids and unesterified cholesterol from hepatocytes, enterocytes, macrophages, and other cells, as well as subsequent esterification by the enzyme lecithin:cholesterol acyltransferase (LCAT). The HDL2 particles shrink in size and liberate lipid-free apoA-I that undergoes either lipidation for regeneration of HDL or glomerular filtration for renal elimination. Secondly, CETP supports the transformation of the triglyceride-rich very low density lipoproteins (VLDLs) into cholesteryl-ester rich LDLs by enhancing the otherwise mainly lipolytic removal of triglycerides and by inducing the accumulation of cholesteryl esters (Figure 1). The physiological importance of CETP for the regulation of VLDL/LDL and HDL metabolism originally emerged from the observation of high HDL cholesterol and low LDL cholesterol in Japanese subjects with homozygous CETP deficiency.

These observations as well as reports on reduced incidence of chronic heart disease (CHD) and increased life expectancy of CETP-deficient patients prompted several pharmaceutical companies to develop CETP inhibitors for the prevention and treatment of atherosclerosis. However, the first clinical evaluation of this concept using the CETP inhibitor torcetrapib recently failed to fulfill the hopes of patients, doctors, scientists, and the pharmaceutical industry. Despite further reducing LDL cholesterol by ~15% and increasing HDL cholesterol by ~50%, the combination of atorvastatin with torcetrapib did not prevent progression of carotid or coronary atherosclerosis more effectively than atorvastatin alone, but produced an excess of cardiovascular and overall mortality. However, it is as yet unknown whether the failure of torcetrapib was caused directly by CETP inhibition or indirectly by off-target effects because torcetrapib also increased blood pressure, by stimulating the synthesis of cortisol and aldosterone independently of CETP inhibition. The researchers involved in the two imaging torcetrapib trials tried to address these questions by post hoc data analyses but they obtained discrepant results: the ILLUSTRATE investigators found a significant regression of coronary atheroma volume in the 25% subgroup of patients who experienced the strongest increase in HDL cholesterol or reached the highest HDL cholesterol levels. In contrast the RADIANCE investigators found correlations of changes in carotid intima-media thickness with changes of LDL cholesterol but not HDL cholesterol.

Thus it is still undecided whether CETP inhibition is a useful target for anti-atherogenic therapy. In fact at least two other CETP inhibitors, anacetrapib and dalcetrapib (formerly designated as JTT705), which do not affect blood pressure and mineralocorticoid synthesis are undergoing clinical evaluation. Like the chemically related torcetrapib, anacetrapib fixes CETP to HDL, irreversibly inhibits CETP by 90%, decreases LDL cholesterol by 15%, and increases HDL cholesterol by 100% at the highest dosage. In contrast, the chemically unrelated dalcetrapib is a

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much milder and reversible CETP inhibitor which interferes with the formation of an important intramolecular disulfide bridge.13

Stein and colleagues have reported the first mid-term follow-up data on the safety and efficacy of dalcetrapib.14 They compared the combination of atorvastatin with either 900 mg of dalcetrapib (instead of the 600 mg phase III dose) or placebo in 135 individuals for their effects on plasma CETP activity, lipids, and (apo)lipoproteins, as well as for adverse clinical effects during 24 and 48 weeks of follow-up. In principal the authors confirmed the findings of previous short-term follow-up studies,13 namely an ~50% decrease in CETP activity, a 30% increase in HDL cholesterol, and a 15% increase in apoA-I with little effect on LDL cholesterol. Importantly, dalcetrapib did not significantly increase the overall rate of side effects.14

These findings are important for the continuation of the already initiated phase III trials which are investigating the effects of the statin–dalcetrapib combination on atherosclerotic plaque load in coronary arteries, endothelial function, and hard clinical endpoints. Until the disclosure of these studies, one can only speculate on the benefits of dalcetrapib and CETP inhibition in general by exploring previous data from observational genetic studies in humans and animals as well as changes in biomarkers observed after treatment with CETP inhibitors.

(i) Japanese carriers of CETP deficiency mutations had a low CHD risk if they had HDL cholesterol levels >2 mmol/L but had a normal or even an elevated risk if they had normal HDL cholesterol levels ranging between 1 and 1.5 mmol/L15,16 or a combination of CETP deficiency and low hepatic lipase activity.17 A recent meta-analysis of 46 studies with data on 27 196 coronary cases and 55 338 controls showed significant associations of three CETP polymorphisms with a decrease in CETP activity and mass by 8–10% and an increase in HDL cholesterol by 4–5% with little reduced cardiovascular risk.18 However, under certain conditions the same polymorphisms were found to increase the cardiovascular risk, e.g. in women or hypertriglyceridaemic subjects19,20 or in patients treated with statins.21 It hence appears that low or high CETP activity influences

Figure 1 Role of cholesteryl ester transfer protein (CETP) in lipoprotein metabolism. Triglyceride-rich VLDLs are secreted by the liver and further metabolized to LDLs by lipolysis of triglycerides (TGs), initially by lipoprotein lipase (LPL) and then by hepatic lipase (HL), and by CETP-mediated enrichment with cholesteryl esters (CEs). HDL metabolism is a multistep process which involves the secretion of lipid-free apolipoproteins by the liver or intestine, the acquisition of phospholipids and cholesterol from cells via ATP binding cassette transporter A1 (ABCA1) and ABCG1, the maturation by lecithin:cholesterol acyltransferase (LCAT)-mediated cholesterol esterification and phospholipid transfer protein (PLTP)-mediated particle fusion, and the final delivery of lipids to the liver, mostly indirectly via CETP-mediated transfer to LDLs. Thereby HDLs become transiently enriched in TGs which, however, are rapidly hydrolysed by HL so that ultimately small HDL particles and lipid-free apoA-I are generated.
cardiovascular risk depending on additional metabolic circumstances such as triglyceride levels and LDL receptor activity. Although not consistent in all studies, the genetic data on reduced statin efficacy in individuals carrying low CETP activity alleles raise questions on the safety and utility of the combination of statins with CETP inhibitors.

(ii) Animal models also provided controversial data on the role of CETP in atherosclerosis. Wild-type mice lack CETP so that only the effect of transgenic CETP overexpression on atherosclerosis could be investigated. In wild-type mice as well as in hypercholesterolaemic mouse models, overexpression of CETP increased atherosclerosis. In contrast, in hypertriglyceridaemic mouse models and in mice overexpressing LCAT, CETP overexpression reduced atherosclerosis despite lowering HDL cholesterol. In rabbits, vaccination against CETP as well as CETP inhibition with either JTT705 or antisense-nucleotides were found to increase HDL cholesterol and reduce atherosclerosis.

(iii) A few studies were undertaken to characterize the functionality of HDL after treatment of patients with either torcetrapib or dalcetrapib. Turnover studies revealed that the changes in the size and concentration of HDL and LDL of patients treated with torcetrapib result from delayed catabolism of apoA-I and HDL and increased clearance of LDL. Whereas the clinical benefit of enhanced hepatic LDL clearance has become evident in many clinical studies and observations, the clinical benefit of delayed HDL catabolism has not. On the one hand the increase in particle number and size may improve the anti-atherogenic potential of HDL, e.g. in stimulating cholesterol efflux from macrophages via the ATP binding cassette transporter G1 and improving endothelial function. On the other hand it is important to bear in mind that CETP inhibition prolongs the half-life of HDL which may make these particles more vulnerable towards oxidative and enzymatic modifications and hence turn them into dysfunctional and rather pro-atherogenic particles. In this regard, one observation of the efficacy study of Stein and colleagues needs further attention: after 24 weeks of treatment patients who received dalcetrapib had significantly higher levels of C-reactive protein (CRP) in their plasma than patients who received placebo. Although this difference disappeared after 24 more weeks of treatment and although the mean level of CRP did not pass the current cardiovascular risk threshold of 2 mg/L this observation may indicate some dysfunctionality of HDL and deserves further studies or post hoc analyses of frozen plasma by the use of more sensitive CRP assays and tests for other inflammatory markers.

Mulling over the odds of CETP inhibition for CHD prevention can be even extended to HDL-modifying therapies in general. It is important to realize that the cholesterol in HDL is neither a protective agent nor a reflection of the anti-atherogenic action of HDL, e.g. in reverse cholesterol transport, but is rather an integrated and indirect estimation of HDL particle size and number. At identical HDL cholesterol levels two individuals may differ considerably in the number, size distribution, and composition of HDL particles and hence atheroprotection. Since HDLs contain dozens of bioactive proteins and lipids with potentially anti-atherogenic activity there is a strong need for biomarkers that better reflect the anti-atherogenicity of HDL than HDL cholesterol or apoA-I concentrations. In addition, any novel HDL therapy must be subject to randomized clinical trials at an early stage to prove that it does not only change the concentrations and composition of HDL but also reduces progression or even induces regression of atherosclerosis and lowers cardiovascular event rates. While scientists and pharmaceutical companies pursuing CETP inhibition and other HDL-modifying therapies as a therapeutic target are to be congratulated for continuing this risky endeavour, I’ll keep my fingers crossed.

Conflict of interest: Arnold von Eckardstein has received consulting fees and honoraria from AstraZeneca, F. Hoffmann-La Roche, and Merck, Sharpe & Dohme.

References


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