

CORONARY ARTERY DISEASE PREVENTION & THERAPY UPDATE

Resurgence of Interest in the Role of HDL / Modulating CETP to Reduce Cardiovascular Risk / dal-VESSEL, dal-PLAQUE & DEFINE Trials

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ABBREVIATIONS

CAD = coronary artery disease
CETP = cholesteryl ester transfer protein
CT = computed tomography
CV = cardiovascular
CVD = cardiovascular disease
FMD = flow-mediated dilatation
HDL = high density lipoprotein
IMT = intima-media thickness
LDL = low density lipoprotein
MRI = magnetic resonance imaging
PET = positron emission tomography
RCT = reverse cholesterol transport (pathway)

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ABSTRACT

The significance of HDL concentration in assessing cardiovascular risk has been recognized over 20 years ago by the Framingham study and it has been subsequently confirmed by other studies and meta-analyses. However, LDL cholesterol has been assigned the cardinal role in cardiovascular (CV) risk management because of its clear etiopathogenic correlation with CV outcome and the efficacy of the drugs used to manipulate its levels in order to change patient prognosis. It is rather recently that HDL has gained the scientific interest once again, with the development of novel agents exhibiting a remarkable ability in raising HDL levels. In this article we comment on the re-emerging role of HDL manipulation with regard to the new CETP inhibitors, under the light of the recent data obtained from large trials assessing their efficacy and safety.

INTRODUCTION

The significance of high density lipoprotein (HDL) cholesterol levels in cardiovascular disease (CVD) progression and outcome has been recognized at least since 1977 based on the results of the Framingham study.¹ More recent data from a meta-analysis of four studies with a total number of over 15000 patients have shown that a 1 mg/dl increase of HDL-C levels is associated with a 2–3% decreased CVD risk.² However, the etiopathogenic correlations are not as well established as between low density lipoprotein (LDL) cholesterol and CVD risk, because in the latter case the relationship is considered causal. On the contrary, HDL levels vary according to numerous other factors, which have been confirmed independent risk factors of cardiovascular disease such as male gender, smoking, obesity, physical exercise, diabetes, systemic inflammation and hypertriglyceridemia.^{3–8} The difficulty of inducing increases in HDL and the limiting side effects of the conventional drugs used for this purpose have rendered HDL a non-primary target of lipid modulation efforts. However, the development of new agents with marked efficacy in raising HDL levels, have provided new pharmacological potential. The cholesteryl ester transfer protein (CETP) inhibitors torcetrapib, dalcetrapib and anacetrapib have gained the scientific interest. However,

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torcetrapid has already been abandoned due to an increase in mortality among the patients randomized to it, but the other two agents are still under investigation with the preliminary results being encouraging and the results of on-going large clinical trials eagerly awaited.

HDL BIOCHEMICAL ROLE AND CETP INHIBITION

HDL can act as an acceptor of cellular cholesterol from peripheral cells that is mediated by lipid transporter molecules such as ATP-binding cassette transporter A1 and G1 (ABCA1 and ABCG1) and scavenger receptor B-I (SR-BI). Subsequently, lipids are delivered to the liver for ultimate excretion into the feces. Moreover, HDL can deliver cholesterol to (V) LDL, which can be taken up via the LDL receptor (LDLr) pathway. The key enzyme catalyzing this procedure is cholesteryl ester transfer protein (CETP).^{9,10} In terms of pure biochemistry this procedure may seem quite clarified. Physiology, however, is more complicated. Some studies show a proportional correlation between HDL concentration and fecal sterol excretion, while others do not.¹¹⁻¹⁴ Interventions aiming at increasing HDL concentration also elicited inconsistent results. The infusion of reconstituted HDL increased sterol excretion while CETP inhibition had a neutral effect despite the marked increase in HDL levels.^{15,16}

The most important contribution of HDL in atheroprotection probably lies in the first step of the reverse cholesterol transport pathway (RCT), which is the lipid transport from lipid-laden macrophages within the vessel wall to the HDL particles. The capacity of HDL to induce cholesterol efflux from the macrophages provides a measure to evaluate HDL-modulating interventions. Again, several trials provide inconsistent results. Torcetrapid has been shown to increase that capacity,¹⁷ yet Chirinos et al demonstrated that patients with recurrent cardiovascular events had unexpectedly high cholesterol acceptor capacity.¹⁸ Studies examining the relation between cholesterol efflux and atherosclerosis progression assessed by carotid intima-media thickness (IMT) measurement and coronary angiography have also produced conflicting results.^{19,20}

Although its role is not yet fully elucidated, HDL exerts beneficial vascular effects by decreasing lipopolysaccharide-induced adhesion of leukocytes to human endothelial cells and inhibiting the expression of endothelial adhesion molecules, LDL-induced monocyte transmigration, LDL oxidation and reactive oxygen species formation.²¹⁻²⁶ Moreover, it has been shown to protect endothelial cells from apoptosis induced by mildly oxidized LDL and it exerts antithrombotic and antiplatelet action via the inhibition of coagulation factors and enhancement of nitric oxide production.²⁷⁻²⁹

For these reasons and on the basis of established epidemio-

logical evidence, despite the current discrepancies observed in the results of several trials, manipulation of HDL still remains an attractive pharmacological aim and a field of continuous and considerable research. Recently the AIM-HIGH trial did not show any clinical benefit in patients with low HDL and high triglyceride concentration who had achieved the target level of LDL and received nicotinic acid on top of statin treatment, despite the favorable change in their lipid profile.³⁰ This much awaited trial was recently terminated by the US National Heart, Lung, and Blood Institute due to futility. No separation of outcome curves between treatment groups could be discerned.

Furthermore, the induction of HDL increase has proven difficult. Statins produce a slight effect on HDL levels and nicotinic acid has a rather limited use because its side effects impair patient compliance significantly. Cholesteryl ester transfer protein (CETP) inhibitors have emerged as exceptionally efficient agents with regards to raising HDL levels, although their clinical usefulness is still under debate. CETP promotes the transfer of cholesteryl esters from HDL to other lipoproteins, such as very low density lipoproteins and intermediate-density lipoproteins and their exchange for triglycerides; subsequently, these cholesterol-enriched lipoproteins can be cleared by the LDL receptor in hepatocytes. However, this pathway may not be perfectly efficient and thus these apo-B particles may remain in the blood and promote atherogenesis. On the other hand, the triglyceride-rich HDL can undergo lipolysis by the hepatic lipase. It has thus been suggested that CETP inhibition will preserve HDL particles, raise HDL cholesterol levels and decrease LDL cholesterol levels.³¹

The first clues regarding the effect of CETP activity on HDL levels came from Japan, where CETP mutations are relatively common. The less the enzyme function, the higher the HDL concentration; however, this did not necessarily correlate with cardiovascular (CV) outcome. At least for certain mutations, the relationship between risk for CAD and serum HDL-C was U-shaped, suggesting that very high serum levels of HDL-C were detrimental.^{32,33}

Trials evaluating the relationship between CETP function and CV risk have also elicited conflicting results. The Women's Genome Health Study, the Veterans Affairs HDL Cholesterol Intervention trial and a large meta-analysis of 92 trials have shown that the single nucleotide polymorphism Taq1B is associated with a per allele rise in HDL-C and a reduction in risk for myocardial infarction. Notably, the homozygous state for the Taq1 B2B2 genotype led to higher baseline levels of HDL cholesterol and a 48% lower rate of cardiovascular events compared to men with the B1B1 genotype.^{34,35} On the contrary, the Copenhagen City Heart Study demonstrated that the loss-of-function polymorphism Ile405 → Val was associated with increased risk for CAD despite higher serum HDL-C, while the gain-of-function mutations A373P and R451Q correlated with a 36% lower risk for CAD despite the low levels of HDL.^{36,37}

In the Prevention of Renal and Vascular End-Stage Disease study, the 629 C > A loss-of function polymorphism was associated with reduced CETP activity, increased serum HDL cholesterol, and increased risk for cardiovascular events.³⁸ Similarly, the REGRESS study, the Framingham Offspring Study³⁹ and the Ludwigshafen Risk and Cardiovascular Health Study of German patients,⁴⁰ all suggested an inverse relationship between CETP activity and risk for CAD-related events.

CLINICAL TRIALS

So far it has become obvious that the relationship between CETP functionality and CVD risk is not linear and a certain level of enzymatic activity probably exists which produces the most beneficial outcome. To elucidate these complicated and confusing data, and to provide robust clinical evidence, pharmacological intervention was undertaken. The first CETP inhibitor to be evaluated was torcetrapib which was ultimately tested in the ILLUMINATE trial.

ILLUMINATE TRIAL

This trial evaluated torcetrapib in clinical events based on previous encouraging results in animal models and early phase studies in humans showing an impressive increase of HDL by 60 to 100% with a contemporary decrease of LDL cholesterol by up to 20%, though it proved inefficient in reducing atheromatous burden in the coronary arteries or carotid IMT.⁴¹⁻⁴⁴

A total of 15,000 stable patients with a history of cardiovascular disease or type II diabetes were randomized to atorvastatin plus torcetrapib 60 mg or atorvastatin alone, after a period of 4-10 weeks of atorvastatin pre-treatment to achieve LDL concentration below 100 mg/dl. The primary outcome was the time to death from coronary heart disease, nonfatal myocardial infarction, stroke or hospitalization for unstable angina. In the torcetrapib group, HDL cholesterol increased by 72.1%, while LDL cholesterol and triglycerides decreased by 24.9% and 9% respectively at 12 months. All these changes were statistically significant. However, the hazard ratio for the primary outcome was 1.25 in the torcetrapib group, as compared with the atorvastatin-only group (95% confidence interval [CI], 1.09 to 1.44; $P = 0.001$). Among the individual components of the composite primary endpoint, death from any cause was also significantly more frequent in the torcetrapib arm. These results led to the premature termination of the study. The exact cause of this unexpected outcome is not fully elucidated. Torcetrapib induces synthesis of both aldosterone and cortisol in adrenal cortical cells.⁴⁵ A rise in blood pressure, attributed mainly to increased levels of aldosterone, and the formation of dysfunctional or even proatherogenic HDL cholesterol particles are considered possible pathogenic mechanisms.⁴⁶

dal-VESSEL TRIAL

Under the realizations made when the results of the ILLUMINATE trial were published, dal-VESSEL was designed to investigate the effects of dalcetrapib on endothelial function, blood pressure, inflammatory markers, and lipid levels. A total of 476 patients with known coronary heart disease or at risk of it and who had achieved the target LDL concentration, were randomized in a double-blind manner to receive dalcetrapib 600 mg/day or placebo for 36 weeks on top of standard therapy (including statins). The two groups were compared over a primary efficacy end point including the change from baseline of flow-mediated dilatation (%FMD) of the right brachial artery at 12 weeks and the 24-hour ambulatory blood pressure monitoring at 4 weeks. The change of FMD at 36 weeks, ambulatory blood pressure monitoring at 12 and 36 weeks, changes in HDL-cholesterol, LDL-cholesterol, triglycerides, CETP activity and standard safety parameters were also assessed as secondary endpoints. Measurements of FMD did not differ significantly between the two arms of the trial after 12 and 36 weeks ($P = 0.1764$ and 0.9515 , respectively). Similarly, ambulatory blood pressure assessment did not reveal any increase in the dalcetrapib receiving patients up to 36 weeks. Activity of CETP decreased by more than 50% in the active treatment group ($P < 0.0001$), and HDL-cholesterol increased by 25, 27, and 31% at 4, 12, and 36 weeks respectively ($P < 0.0001$). Interestingly, LDL levels did not change. Among the biomarkers of inflammation, oxidative stress, and coagulation only Lp-PLA(2) mass levels increased by 17%. The number of clinical events was the same in both study groups. Based on these results, dalcetrapib can be considered a tolerable and safe agent which increases HDL-cholesterol levels without affecting nitric oxide-dependent endothelial function, blood pressure, or markers of inflammation and oxidative stress.⁴⁷

dal-PLAQUE TRIAL

This study, included clinically stable patients with previous known coronary heart disease or at high risk of coronary heart disease (diabetes or a 10-year risk of coronary heart disease events >20% by Framingham Risk scoring), triglyceride concentrations of 400 mg/dL or lower (≤ 4.5 mmol/L), and PET/CT index of carotid or aortic arterial wall (target) to background (blood) ratio (TBR) of 1.6 or higher, as identified by ¹⁸F-FDG uptake measured by PET/CT. They received hypolipidemic medication other than fibrates or nicotinic acid to maximal tolerated dosage or that achieving LDL-cholesterol level below 100 mg/dl. Finally, 130 patients were randomized in a 1:1 ratio to receive either dalcetrapib 600 mg/day or placebo for 24 months. The primary MRI endpoint was the change in total vessel area, wall area, wall thickness, and wall area/total vessel area ratio (normalized wall index) expressed as absolute or percent difference, or both after 24 months. The same variables served as secondary endpoints when assessed

in 6 and 12 months. The primary PET/CT endpoint was the change in arterial wall ^{18}F -FDG uptake (assessed as the TBR) after 6 months, a measurement assessing vascular inflammation. Biochemical indices' change after 3, 12, and 24 months, such as C-reactive protein (hsCRP), lipoprotein-associated phospholipase A2 (Lp-PLA2), interleukin 6, soluble P-selectin (sP-selectin), soluble E-selectin (sE-selectin), soluble intracellular adhesion molecule, soluble vascular cell adhesion molecule, matrix-metalloproteinase 3 and 9, myeloperoxidase, tissue plasminogen activator, and antigen and activity of plasminogen activator inhibitor 1 were also taken into account as complementary endpoints. Total vessel area was significantly reduced in the dalcetrapib group at 24 months (-4.01 mm^2 , 90% CI -7.23 to -0.80 , $p=0.04$). The other indices were not different. Concentrations of HDL-cholesterol increased by 31% and those of apolipoprotein A1 increased by 10% at 24 months in the dalcetrapib-receiving subjects. As far as the PET/CT primary end point of most-diseased-segment TBR of the index vessel is concerned, mean change from baseline was -0.26 (SE 0.08) for placebo and -0.19 (SE 0.08) for dalcetrapib ($p=0.51$). Thus, no evidence of increased vascular inflammation with dalcetrapib compared with placebo was noticed. However, in the carotid arteries average most diseased-segment TBR was significantly reduced only in the dalcetrapib group but compared with placebo, this reduction was non-significant. In the whole study population, increases in HDL-cholesterol did not correlate with structural changes in the vessels as assessed by MRI, while they were associated with decreases in TBR-assessed arterial inflammation ($p=0.04$). More specifically, a 4.3% reduction in most-diseased-segment TBR was recorded with every increase in HDL-C tertile. However, due to the extreme heterogeneity of the tertiles with respect to the therapy given, since the lowest tertiles represent patients in the placebo group and the highest ones lie in the dalcetrapib group, the relative influence of HDL levels is not possibly clarified. No significant differences were reported in terms of drug discontinuation or adverse events between the two groups. In conclusion, in this trial, dalcetrapib seems to cause no short term harm and can possibly decrease adverse structural changes within the vessels by reducing vascular inflammation and increasing HDL-cholesterol concentrations.⁴⁸

DEFINE TRIAL

This trial aimed at assessing the efficacy and safety of anacetrapib in patients already in statin therapy who had achieved the target LDL cholesterol levels and had HDL levels below 60 mg/dl. The 1623 patients with known coronary heart disease or at high risk for coronary events (Framingham Risk score of $>20\%$ per 10 years) were randomized to either 100 mg of anacetrapib daily or placebo on top of statin administration and the two groups were compared with regard to percentage changes of LDL in 24 weeks. The change in LDL, HDL, non-HDL cholesterol, apolipoprotein B, and apolipoprotein

A-I concentration at 24 and 76 weeks were also evaluated. The safety end point required assessment of adverse events, laboratory testing related to safety (hepatic biochemistry, electrolyte and aldosterone levels, markers of muscle damage), assessment of vital signs, cardiovascular outcome and death throughout the 76-week treatment period. The primary efficacy end point was met; LDL decreased from 81 mg/dl to 45 mg/dl in the anacetrapib group, as compared with a change from 82 mg/dl to 77 mg/dl in the placebo group which represented a significant 39.8% reduction ($P<0.001$) at 24 weeks. Similar results were obtained for HDL concentration which increased by 138.1% (41 mg/dl to 101 mg/dl compared with 40 mg/dl to 46 mg/dl in the placebo group $P<0.001$). The other lipid variables showed significant improvement as well and all these changes were maintained until the end of the study follow-up at 76 weeks. The safety end points, laboratory or clinical, did not differ between the two groups. The exact incidences suggest, through a Bayesian analysis, that there is a 94% predictive probability that the 25% increase in cardiovascular adverse events that was seen with torcetrapib will not be the case with anacetrapib also.⁴⁹

CONCLUSION

In conclusion, CETP inhibition represents the single most efficient way to raise significantly HDL concentration. However, it remains in doubt whether this biochemical modulation will be translated to clinical benefit. The first agent of the category, torcetrapib, failed to improve prognosis; on the contrary it increased mortality because it promoted aldosterone synthesis and raised blood pressure. The novel members dalcetrapib and anacetrapib have demonstrated a favorable safety profile and hopefully they will not exert the adverse outcome observed with their ancestor. The early studies suggest they improve the lipid profile with regard to both HDL and LDL levels, and dalcetrapib may also be efficient in terms of vascular atheroprotection. A large trial with clinical endpoints is currently being conducted (dal-OUTCOMES) and its results are expected to enlighten the field and determine the final role of CETP inhibition in cardiovascular risk management.

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