Cholesterol ester transfer protein inhibition in prevention of cardiovascular disease: the end of the promising story?

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As high-density lipoprotein (HDL) cholesterol is strongly and inversely related to atherosclerotic cardiovascular disease (CVD), and current LDL lowering therapeutic strategies do not reduce risk in a substantial proportion of CVD patients, strategies to increase HDL have been increasingly attracting attention. Among the new strategies proposed, inhibition of cholesterol ester transfer protein (CETP) has been suggested as an effective tool to increase HDL levels. However, despite an impressive effect on increase in HDL and decrease in LDL, results of the three published clinical trials (ILLUSTRATE and RADIANCE 1 and 2) with CETP inhibitor torcetrapib together with prematurely stopped ILLUMINATE trial showed disappointing clinical results (1 – 3). The ILLUMINATE trial was stopped because of an excess of deaths, myocardial infarction, angina, revascularization procedures and heart failure in patients receiving torcetrapib (4) and the other three trials did not show a decrease in the progression of atherosclerosis evaluated by carotid intima-media thickness and intravascular ultrasonography. Hypertensive effect, possible activation of the renin-angiotensin system, vasospasm, off-target toxic effects and non-functional HDL particles produced by CETP inhibition have been suggested as contributors to the failure of CETP inhibitor torcetrapib (4).

Torcetrapib reduces the transfer of cholesteryl esters (CE) from HDL to apoB containing lipoproteins, decreases their concentration and increases the concentration of HDL in plasma. Increase of HDL concentration with torcetrapib is due to reduction of HDL-apoAI catabolic rate rather than to an increasing production of it (5). A shift in HDL to larger size (α1-migrating HDL) has also been shown with the treatment (5, 6).

The destination of newly produced CE in plasma by the action of lecithin cholesterol acyltransferase (LCAT) appears to be more essential for the origin of atherosclerosis than their total production (7, 8). This hypothesis is supported by the evidence that part of the newly produced CE (produced mainly in small particles of HDL) is transported by means of CETP to VLDL in exchange for TGs and, through the lipolytic cascade, to LDL. Another part of the CE remaining on HDLs is transferred to the cell-surface scavenger receptor class B type I (SR-BI), which mediates selective HDL-CE uptake into cells. These two destinations differ in their impact on atherogenic risk: the HDL pathway into SR-BI is considered an antiatherogenic pathway, whereas the CETP pathway into VLDL appears to be proatherogenic. The choice of pathway is mainly affected by the size of the HDL population: the small HDL particles increase the cholesterol esterification rate and route CE through VLDL, while the large buoyant particles reduce the speed and transfer CE via SR-BI. Differently sized lipoprotein particles play a protective (buoyant HDL and LDL particles) or an atherogenic role (small HDL and LDL particles) in cardiovascular disease.

Thus the question why the increased amount of large HDL does not fulfill its protective anti-atherogenic role remains unanswered. Either remodeled large HDLs are not identical with HDL_{2b} protective subpopulation and have no reasonable capacity to transport newly produ-

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ced cholesteryl esters to the catabolic destinations, or reduction of HDL-apoAI catabolic rate restrains CE to be catabolized at proper sites. Also it is not clear whether esterification of cholesterol by LCAT is affected.

Moreover, creation of abnormal HDL particles can result in their proinflammatory and proatherogenic properties (9, 10).

Functional testing of lipoprotein quality, such as the assay of fractional esterification rate of cholesterol in HDL plasma (FER_{HDL}) which reflects the distribution of HDL and LDL subpopulations and HDL functionality may help the understanding of metabolic changes induced by CETP inhibitors (8). This functional biomarker correlates highly with the simplest algorithm (in different studies r = 0.7 – 0.9) – Atherogenic Index of Plasma (AIP) as a logarithmically transformed ratio of molar concentrations of triglycerides (TG) to HDL cholesterol (11). The association of AIP with lipoprotein particle size is intelligible as TGs participate in the production of the population of small, dense LDLs and have also been proposed to be the major determinant of cholesterol esterification/transfer and HDL remodeling in human plasma (8). Both, FER_{HDL} and AIP directly relate to other biochemical and clinical parameters of CVD risk such as a highly significant correlation with apoB, apoCIII, apoE and inverse correlation with apoAI. FER_{HDL} and AIP also have been shown to be best predictors of positive findings on coronary angiography (12).

It has been shown that another CETP inhibitor – JTT-705 lowers FER_{HDL} value in rabbits, which reflects increased protective HDL_2 particles (13). However, rabbits are deficient in hepatic lipase and thus may not rely on the CETP-hepatic lipase interaction to regenerate lipid-poor apoA-1 for interaction with ABCA1, and thus may not exactly reflect human metabolism.

All four torcetrapib trials compared combined regiment of torcetrapib plus atorvastatin against atorvastatin alone as a control group. Can we hypothesize torcetrapib-atorvastatin interaction shifting lipid metabolism towards a different metabolic pathway when compared to CETP inhibition alone? Torcetrapib reduces the transfer of cholesteryl esters from HDL to apoB containing lipoproteins, decreases their concentration and increases concentration of HDL in plasma. Millar et al. (14) showed that when used alone, torcetrapib reduces VLDL, IDL, and LDL apoB100 levels primarily by increasing the rate of apoB100 clearance. In contrast, when added to atorvastatin treatment, torcetrapib reduces apoB100 levels mainly by enhancing VLDL apoB100 clearance and reducing production of IDL and LDL apoB100. Perhaps even other, less favorabel lipids' pathway changes due to torcetrapib/atorvastatin effect interaction, can play a role in the case.

As suggested by Nissen et al. (1), it is difficult to determine the extent, to which the failure of torcetrapib was the result of dysfunctional HDL cholesterol, properties that increased blood pressure, or other toxic effect specific to this agent. Other CETP inhibitors did not show blood pressure increasing properties (15). Therefore, the failure of a single class drug with a pro-hypertensive effect does not automatically means that CETP inhibition with other agents will be useless or even harmful. However, it is necessary to clearly understand the effect of such agents on HDL composition, functionality and on possible toxic effect(s) suggested by the torcetrapib case.

What can we learn from the torcetrapib studies? Even from "negative" results there is a strong and important message coming from the trials – as pointed out by authors (1), intravascular ultrasonography and other imaging techniques would not be sensitive enough to detect nonatherosclerotic vascular toxicity or other safety problems. Studies using surrogate markers can thus provide only limited information on the effectiveness of new interventions and their mechanism of action and, therefore, data from hard clinical end-point studies are crucial for demonstrating the favorable effect of any new drug.

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