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The cholesteryl ester transfer protein (CETP) promotes the transfer of cholesteryl esters (CE) from high density lipoproteins (HDL) to apoB-containing lipoproteins, one of key steps of reverse cholesterol transport and its inhibition thus increases the concentration of HDL cholesterol while decreasing the cholesterol level in apoB-containing lipoproteins. The concept that CETP inhibition may prevent atherosclerosis because of these effects has been investigated, with varying results. Cardiovascular clinical outcomes studies of the first three CETP inhibitors were terminated because of either increased mortality or futility despite marked increases in HDL-cholesterol, although in each case there were problems with either serious adverse effects unrelated to CETP (torcetrapib) or to trials that may have terminated too early (dalcetrapib and evacetrapib). A fourth trial (REVEAL) using the CETP inhibitor anacetrapib was larger and much longer and showed that inhibition of CETP does reduce coronary events (the primary endpoint of the trial), although the benefit may have been the consequence of a reduction of cholesterol levels in the atherogenic apoB-containing lipoproteins rather than an increase in HDL levels. Anacetrapib is retained in the body for years after therapy and, although there were no serious adverse effects of the drug in the REVEAL trial, a decision was made to not develop the agent further. So, the future of CETP inhibition as a strategy to reduce cardiovascular events in statin-treated patients remains uncertain.

However, it should be emphasized that the results of the CETP inhibitor trials do not necessarily mean that HDL particles do not protect against atherosclerosis. Rather, the trials may mean only that raising levels of cholesteryl ester in HDL particles by CETP inhibition does not protect against atherosclerosis, with any possible benefit resulting from a reduction in the cholesterol level in the atherogenic apoB-containing lipoproteins.

I would like to encourage the members of IAS to reevaluate the role of HDL metabolism in cardioprotection, especially focusing on the role of HDL in reverse cholesterol transport.