Risk Factor Management: Role of HDL

This department covers selected points from the 2009 Endocrine Update: A CME Day from the Division of Endocrinology and Metabolism at McMaster University and the University of Western Ontario.
Program Chairs: Aliya Khan, MD, FRCPC, FACP, FACE and Terri Paul, MD, MSc, FRCPC

Sultan Chaudhry, BHSc

High levels of LDL-C and low levels of HDL-C have been shown to independently increase the risk for CVD.[1] Low HDL-C levels together with increased triglycerides and increased levels of small, dense atherogenic LDL particles are often the characteristic lipid profile in Type 2 diabetes and may partly explain the high correlation found between diabetes and CVD.[2-4]

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Even though much evidence has been reported on the inverse relation between HDL-C levels and CVD, the role of raising HDL-C levels to specifically lower CVD is still under much controversy. The unexpected failure of cholesteryl ester transfer protein (CETP) inhibitor in 2006 has left many confused as to the true benefit of raising HDL-C levels. Several trials showed this particular CETP inhibitor's inability to beneficially alter CVD surrogate endpoints despite raising HDL-C and lowering LDL-C levels[5,6] and one study even demonstrated increased CV events with its use.[7]

To understand why these results possibly came to be, it is important to be reminded of the structure of the HDL particles which are heterogeneous and differ in shape, size, content and properties from each other. Some may have more antioxidant and anti-inflammatory properties and thereby be more atheroprotective. Thus, HDL-C levels are not a reliable indicator of the actual number of HDL particles nor HDL functionality or atherogenic potential.[8] Another reason why this specific CETP inhibitor may have led to higher CVD events is because the drug is associated with an increase in BP.[5-8] This BP effect has not been seen with other CETP inhibitors such as anacetrapib.[9] It is thus possible that the failure of this specific CETP inhibitor is likely due to the molecule itself rather than its mechanism of action; however, we will need to await the results from randomized controlled trials of these other CETP inhibitors on CVD events.

There are currently a few non-pharmacologic interventions available to increase HDL-C levels. Decreasing triglyceride levels through lifestyle modification such as improved glycemic control, use of diets low in fat and simple carbohydrates and alcohol reduction can improve HDL-C levels; smoking cessation, weight loss and exercise

can also increase HDL-C levels.[10] There are a handful of pharmacological interventions available including niacin that is effective in raising HDL-C levels and is associated with decreased CVD.[11] Patients may be more willing to consume niacin as it is a vitamin, but its main side-effect of flushing often is a barrier to its use. Fibrates can also modestly increase HDL-C and lower LDL-C levels and has demonstrated CVD benefits in those with low HDL-C levels.[12] Newer HDL-based therapies include infusion of Apo A-1 Milano variant which has been found to decrease CVD by increasing the functionality of HDL. Other CETP inhibitors such as dalcetrapib and anacetrapib are currently in clinical testing as they have not demonstrated pressor effects as this specific CETP inhibitor did.

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Overall, although LDL-C is the primary treatment target for diabetes, HDL-C still remains an important secondary target. HDL metabolism is complex and the role of HDL in CVD should not be questioned based on the failure of torcetrapib. There are currently a few non-pharmacological and pharmacological interventions for raising HDL-C, but in the future, better tolerated and more effective options are needed. Dx

Dr. Chaudhry is an MD/PhD Candidate, the Michael G. DeGroote School of Medicine & Medical Sciences, McMaster University, Hamilton, Ontario.

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