EBM Tools for Practice:
"HDL-P vs. ApoA1 vs. HDL-C" in Context of the HDL-Hypothesis Controversy

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Recent high-profile interventional studies and a large genetic association analysis have failed to show a benefit of raising high density lipoprotein cholesterol (HDL-C) levels on cardiovascular disease (CVD) outcomes, calling into question the validity of the HDL hypothesis. Among several plausible explanations for these findings, one is that assaying the cholesterol content of HDL (HDL-C) may fail to adequately measure its protective effects. Two potentially better ways to assess the protective effects of HDL are to measure levels of the major HDL apolipoprotein (apo), ApoA1, and to estimate HDL-particle number (HDL-P) by nuclear magnetic resonance (NMR).

The "Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health" (AIM-HIGH) study failed to show CVD benefit from HDL-C raising with niacin.[1] The lack of benefit of niacin in this trial was surprising given the many pre-AIM-HIGH studies demonstrating that niacin reduces CVD events.[2] In patients with low HDL-C and stable coronary artery disease, extended release nicotinic acid (ERNA) was added to statin therapy and subsequent CVD events were assessed. To better understand the impact of the HDL-C raising effect of ERNA, low density lipoprotein-cholesterol (LDL-C) was targeted to 40-80 mg/dL in both groups, leading to higher statin doses and more frequent ezetimibe use in the control group. Low-dose immediate-release nicotinic acid (IRNA) was given to the control group to cause flushing and maintain the study blind. Possible explanations for the surprising lack of CVD benefit included (1) near equalization of LDL-C levels (weighing against the HDL-hypothesis), (2) smaller-than-expected HDL-C difference of only 15% due to IRNA in the control arm, and (3) the short study duration of only 2 ½ years[3] (neither (2) nor (3) weighing against the HDL-hypothesis). Further, in a post hoc subgroup analysis in subjects having both high triglycerides and low HDL-C at baseline, there was a statistically significant 37% decrease in CVD events with high-dose ERNA vs. control. This finding clearly supports the traditional HDL hypothesis.[4] An alternative explanation for the surprising results of AIM-HIGH is that the lack of CVD benefit with ERNA was expected since, despite a robust increase in HDL-C and ApoA1 with ERNA, HDL-P may not increase with ERNA treatment.

Another study with results appearing to weigh against the HDL hypothesis is the "Randomized, Double-blind, Placebo-controlled Study Assessing the Effect of RO4607381 on Cardiovascular Mortality and Morbidity in Clinically Stable Patients With a Recent Acute Coronary Syndrome" (dal-OUTCOMES) trial.[5] In this study, dalcetrapib, a cholesteryl ester transfer protein inhibitor (CETP-I), failed to lower CVD events despite increasing HDL-C by 31%, (and previously

being reported to raise ApoA1 by 13%, and HDL-P by 9%).[6] The apparent contradiction of the HDL hypothesis in dal-OUTCOMES (by 3 HDL metrics) might be explained, however by consideration of two study findings: (1) a modest inverse trend between CVD risk and the degree of HDL-C increase with dalcetrapib (suggesting that the increase in HDL-C remained somewhat protective), and (2) a statistically significant increase in blood pressure with dalcetrapib (suggesting that the lack of overall CVD benefit was due to modest adverse adrenal effects, analogous to much greater ones seen with another CETP-I, torcetrapib). Ongoing laboratory and statistical analyses may better explain the apparently paradoxical results of dal-OUTCOMES.

A third very recent clinical trial result also seems to weigh against the HDL hypothesis. According to a preliminary report of The Heart Protection Study-2 (HPS-2), ERNA (with a flush-blocker, laropiprant) added to a statin failed to reduce CVD vs. statin alone.[7] Certain problems with the AIM-HIGH clinical trial design were avoided. No IRNA was given to control subjects in HPS-2, since the lack of flushing in the treatment arm did not require flushing in the control arm to maintain the study blind. Also HPS-2 was much larger and longer than AIM-HIGH. Unfortunately, however, baseline HDL-C and triglyceride levels in HPS-2 were even closer to normal than they were in AIM-HIGH. Analyses of HPS-2 subjects with low HDL-C and high triglycerides might show decreased CVD risk similar to the subgroup analysis in AIM-HIGH, which would provide further support for the HDL hypothesis in those important patients.

Beyond these randomized pharmaco-therapeutic trials, a recent Mendelian randomization study also examined the relationship between HDL-C levels and CVD risk.[8] A single nucleotide polymorphism in the endothelial lipase gene was associated with HDL-C levels 5.5 mg/dL (roughly 12%) higher than in non-carriers. Surprisingly, this was not associated with a lower myocardial infarction (MI) rate. Importantly, however, the higher HDL-C was not accompanied by a lower triglyceride level (in contrast to the inverse relationship seen in the general population). Further, polymorphisms in 14 other genes with isolated HDL-C increases (no triglyceride change) also failed to reduce MI. Unfortunately, neither ApoA1 nor HDL-P levels were reported in that study.

As noted above, some of the evidence weighing against the HDL hypothesis might be explained by using different measures of HDL plasma concentration. ApoA1 seems to play many important roles in atheroprevention, and its level is inversely related to CVD, as strongly, or more strongly than HDL-C in many epidemiological studies.[9,10] Similarly, HDL-P, a measure of HDL particle concentration independent of both HDL-C and ApoA1, may inversely predict atherosclerosis and CVD as well or better than does HDL-C.[11,12] An interesting example of this independent prognostic ability comes from a recent analysis from the prospective observational Multi-Ethnic Study of Atherosclerosis (MESA).[13] HDL-P and HDL-C were both strongly inversely associated with carotid intima-media thickness (CIMT) and incident coronary heart disease (CHD), but the relationship with HDL-C was greatly weakened after adjusting for HDL-P and LDL-P (an estimation of LDL particle concentration from NMR). In contrast, adjustment for HDL-C and LDL-P did not affect the relationship of HDL-P with CIMT and CHD. The independence of HDL-P from other lipid/lipoprotein measures is further demonstrated by the fact that it appears to be the only HDL parameter consistently neither increased by niacin treatment nor decreased by high plasma triglyceride levels.

HDL-P was also independent from other HDL parameters in a Mendelian randomization analysis of genetic polymorphisms in the phospholipid transfer protein (PLTP) gene. In this study PLTP-related HDL increases were associated with decreased CVD rates.[14] HDL-C was only modestly and non-significantly increased, whereas HDL-P (especially small HDL-P) was significantly increased and inversely related to CVD.

Although several measures of HDL levels can inversely predict CVD, a dynamic measure of HDL function, such as reverse cholesterol transport (RCT) intuitively might provide even better predictive ability. A recent study by Khera, et al. demonstrated that assaying one aspect of HDL function (cholesterol efflux from cultured cells, related to the first step in RCT) was somewhat more predictive of CIMT and angiographic coronary artery disease than was HDL-C.[15]

This is a challenging time in the evolution of our understanding of the roles of HDL in atherogenesis and CVD risk. Recent studies suggest reconsideration not only of the HDL hypothesis, but also of the optimal methods to measure potential HDL-mediated beneficial effects on atherosclerosis and CVD events. HDL-C measurements are still clinically useful, but adding independent measures of HDL levels such as ApoA1, HDL-P and possibly assays of HDL function, may provide even better prediction of CVD risk. The HDL hypothesis remains "alive and (presumably) well" for now, even though much additional research is needed to validate old and new diagnostic and therapeutic tools to better assess and enhance the many apparently favorable effects of HDL on atherosclerosis and CVD. ■

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