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HDL and Cardiovascular Risk:

Time to Call the Plumber?

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Abstract

High-density lipoprotein cholesterol (HDL-C) has been dubbed the good cholesterol because it is thought to reflect the ability of HDL particles to remove excess cholesterol molecules from peripheral cells (including those in atherosclerotic plaques) for return to the liver. Not surprisingly, then, HDL-C has frequently been assumed to be a biomarker of HDL function, consistent with the inverse relationship in observational studies between plasma levels of HDL-C and risk of coronary artery disease. Recently, Voight et al have challenged this assumption by showing that genetically elevated HDL-C did not protect against myocardial infarction. This finding has fueled a lively discussion in the lay, scientific, and medical press about the relationship between HDL-C and HDL function, and the potential effectiveness of various HDL-C raising strategies.

Epidemiological studies clearly show that levels of high-density lipoprotein cholesterol (HDL-C) are inversely associated with the risk of coronary artery disease and its thrombotic complications.[1] However, in a recent study, Voight et al[2] tested the hypothesis that increased plasma HDL-C is protective for myocardial infarction (MI) by examining the relationship between genetic variations associated with elevated levels of plasma HDL-C and the risk of MI.[2] The major approach used was Mendelian randomization, a method developed to infer disease causality of a genetic variation.[3] In the first test of the hypothesis, a loss of function single nucleotide polymorphism (SNP) in the endothelial lipase gene (LIPG Asn396Ser; minor allele frequency 2.6%) that is associated with an elevated mean plasma level of HDL-C (but no change in the plasma level of low-density lipoprotein cholesterol [LDL-C] or triglycerides) was evaluated in 20 913 MI cases and 95 407 controls. Although carriers of LIPG Asn396Ser had 0.14 mmol/L (5.5 mg/dL) higher mean plasma levels of HDL-C (with similar levels of other lipid and nonlipid risk factors for MI) compared with noncarriers, no significant effect on risk of MI was observed. In the second test of the hypothesis, the authors generated a genetic score by combining 14 SNPs that are associated with HDL-C in 12 482 MI cases and 41 331 controls. A 1-SD increase in HDL-C because of the genetic score did not lead to a change in the risk of MI. From these 2

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analyses, the authors concluded that some genetic mechanisms that raise plasma HDL-C do not necessarily lower the risk of MI and that the findings challenged the concept that raising of plasma HDL-C will uniformly translate into reductions in risk of myocardial infarction.

This negative conclusion about the benefit of raising HDL-C is consistent with recent studies in which the plasma level of HDL-C was raised pharmacologically (eg, ILLUMINATE,[4] AIM-HIGH,[5] and dal-OUTCOMES[6]) without evidence that there were any reductions in cardiovascular events. Not surprisingly, these studies, and others noted below, have called into question in the medical and lay press the HDL hypothesis. Indeed, even experts in the lipoprotein field have started to voice doubts about the HDL hypothesis. At a recent Gordon Conference on Lipoprotein Metabolism, for example, one savant asked "Is HDL in the toilet?"; thereby inspiring the title of this commentary.

The results of Voight et al are strengthened by their consistency with previous Mendelian randomization studies, as noted in the editorial comment that accompanied the article.[7] The fundamental principle of this approach is that the random assortment of alleles during gametogenesis leads to a distribution of genetic variants that is independent of typical confounders of observational studies, such as behavioral or environmental factors.[8] In a study involving 54 500 individuals from the Copenhagen City Heart Study (CCHS) and the Copenhagen General Population Study, low HDL-C levels (associated with a genetic variant of lecithin-cholesterol acyltransferase) were not linked to increased risk of MI, whereas the epidemiological data showed a robust association.[9] Similarly, genetic variants of apoA-I (the major protein in HDL), which were associated with higher levels of apoA-I (up to 6.6%) and HDL-C (up to 8.5%) in the CCHS population, were not associated with decreased risk of MI.[10] In addition to the consistency among these Mendelian randomization studies, the results in Voight et al are further strengthened by their data on the HDL-C genetic score composed of 14 common SNPs in the study population, which as noted above was also negative. In contrast, a 1-SD increase in LDL-C because of its genetic score (based on 13 SNPs) significantly increased the risk of MI, consistent with estimates from observational studies and with the causal connection between plasma LDL-C levels and MI in numerous intervention trials.

For those who still think that raising HDL-C has the potential to reduce MI risk, it is tempting to speculate that for many of the genetic variations studied to date, the associated changes in the HDL-C levels were, at most, modest. The largest effect in Voight et al, for example, was for the endothelial lipase SNP; the average increase in HDL-C was 5.5 mg/dL (although based on estimates from epidemiological data, would have been predicted to result in a 13% risk reduction for MI, a change that the study was statistically powered to detect). Unfortunately, a number of intervention trials have not been encouraging on this point. In particular, the present study comes on the heels of Roche withdrawing from the HDL-C raising arena after its dal-OUTCOMES[6] study with the cholesteryl ester transfer protein inhibitor dalcetrapib failed to show clinical benefits. This was despite inducing a >30% increase in HDL-C. Two possibilities invoked for this lack of success were that the increase in the HDL-C level was still insufficient and that dalce-trapib has a minimal effect on LDL-C level.[11] In this regard, a meta-analysis of statin intervention trials, in which the end point was plaque size determined by intravascular ultrasound, showed that the lipoprotein profile for the best outcome was LDL-C lowering and HDL-C raising,[12] a scenario not tested in Voight et al, because of the focus on isolated changes in HDL-C. Nonetheless, another cholesteryl ester transfer protein inhibitor, torcetrapib (Pfizer), which had greater HDL-C raising effects than dalcetrapib and a significant lowering effect on LDL-C, also failed to provide benefit, and even showed evidence in the ILLUMINATE[4] trial of causing excess deaths from cardiovascular and other diseases in the treatment group.

The failure of torcetrapib, despite raising HDL-C by 72% was subsequently attributed to molecule-specific (non–class-related) off-target effects (such as increased blood pressure and low serum potassium) related to the stimulation of aldosterone production. A ray of hope for the HDL-C protection concept came from a post hoc analysis of ILLUMINATE, which showed that cardiovascular events were lower in the torcetrapib-treated group with the highest increases in HDL-C and apoA-I.[4] The issue of whether cholesteryl ester transfer protein inhibitors can be useful clinical therapies will be more definitively addressed in the ongoing trials with the anacetrapib (Merck) and evacetrapib (Eli Lily) compounds, which appear to be free of the off-target effects of torcetrapib. Nevertheless, because both compounds significantly lower LDL-C, a direct test of the HDL-C raising hypothesis will not be possible, but perhaps statistical analyses to determine whether there is any benefit beyond what is expected for the degree of LDL-C lowering will provide indirect support.

Another blow to the proposition that raising HDL-C will lower MI risk has come from the niacin-based Atherothrombosis Intervention in Metabolic Syndrome with Low HDL Cholesterol/High Triglyceride and Impact on Global Health Outcomes (AIM-HIGH)[5], despite niacin's effectiveness in reducing cardiovascular events in the HATS[13] trial, although this was smaller and of different design. AIM-HIGH has been criticized on a variety of fronts[14] giving hope to those awaiting the results from the large Merck-sponsored Heart Protection Study 2—Treatment of HDL to Reduce the Incidence of Vascular Events (HPS-2 THRIVE, ClinicalTrials.gov Identifier: NCT00461630), a trial of extended release niacin. Problems with any niacin trial, however, are the lipid changes (lowering of LDL-C and triglycerides) concomitant with the mild elevation of HDL-C, which will unavoidably complicate the testing of the HDL hypothesis.

Although we have mentioned that, at least in some studies, the HDL-C rise was modest at best, suggesting a threshold effect, this line of reasoning is incomplete and overly simplistic. A rise in HDL-C may indeed be a biomarker of increased reverse cholesterol transport (RCT; the process whereby HDL picks up cholesterol from peripheral cells and returns it to the liver). RCT is widely thought to be a beneficial pathway, but its relationship to plasma levels of HDL-C is likely to vary depending on the metabolic circumstances, as especially established in preclinical models. For example, when hepatic levels of the membrane protein scavenger receptor BI were raised in mice, the ability of HDL particles to unload cholesterol to the liver increased and plasma levels of HDL-C actually declined.[15,16]

Even if we restrict our attention to HDL particles themselves, and not the many factors with which they interact to accomplish RCT, it is clear that HDL-C is not necessarily reflective of the broad heterogeneity in size, structure, lipid and protein composition and metabolism that is increasingly recognized to characterize this class of lipoproteins.[17] For example, there are a number of density and size subclasses of human HDL particles, and starting with the original, low resolution, categorizations (HDL_2, HDL_3), different degrees of atheroprotection have been speculated for each subclass.[18] It is also well recognized that dozens of protein components, some of which are thought to be pro- or antiatherothrombotic, are carried on HDL particles,[19] implying significant particle diversity in terms of composition (since no single particle carries every protein) and potential benefits. In clinical studies, this heterogeneity, especially with respect to atheroprotective function, is becoming apparent. For example, the protein makeup of HDL appears to be altered in patients with coronary artery disease.[19] Furthermore, in the post hoc analysis of the IDEAL and EPIC Norfolk studies, high HDL-C levels and large HDL particle size were associated with increased coronary artery risk, whereas levels of apoA-I (which, in the form of small, lipid-poor HDL particles is the preferred acceptor of ABCA-1 mediated cholesterol efflux) remained negatively associated.[20] Related to these findings is a recent clinical study

showing that the ability of HDL to efflux cholesterol in an ex vivo assay was not correlated with HDL-C, but with cardiovascular disease risk.[21]

Preclinical data indicate that, in addition to RCT, HDL particles exert anti-inflammatory, antioxidant, and antithrombotic effects—functions not necessarily related to HDL-C, and which would be expected to vary among individuals.[22] In parallel to the apparent demise of HDL-C as a strong causal biomarker of protection from MI, then, is the rise of the concept of functional and dysfunctional HDL particles in terms of their effects on RCT and other potential modulators of atherosclerosis pathophysiology. This expanded view of HDL is not new,[23] but as analytical techniques and assays have advanced, the experimental evidence has multiplied over time, as have the ways in which HDL may be dysfunctional. By this reasoning, a modification of HDL particles that disrupts a protective function would not be expected to be beneficial, and even worse, may even be harmful, independent of changes in the total plasma level of HDL-C. In this light, it is not surprising that endothelial lipase-associated increases in HDL-C were not associated with decreased MI risk, given that endothelial lipase modifies HDL particles and that there were no compelling data, as the authors note, in mouse models that raising plasma levels of HDL-C via endothelial lipase deficiency protected against atherosclerosis.

As noted earlier, the second Mendelian randomization study in Voight et al involved a score based on genetic variants associated with increased plasma levels of HDL-C, but these genes included known or potential modifiers of HDL particles, such as *LCAT* and *ANGPTL4*, suggesting the possibility that dysfunctional aspects of HDL particles were a consequence of the action of their gene products. A review of the literature provides more direct ammunition to bolster the reputation of HDL, especially from studies in which increasing the production or availability of functional HDL particles was accomplished. Many of these studies are preclinical, with the core strategy being mainly the increased production by the liver of apoA-I by either transgenic or viral-vector means; increasing the number of HDL particles in this manner resulted not only in delayed progression of atherosclerosis, but also in the promotion of its regression.[24] In many of these reports, a consistent finding has been a reduction in macrophage/lipid content of the plaque, an increase in plaque collagen, and a phenotypic switch from proinflammatory M1 macrophages to anti-inflammatory M2 macrophages.[25–28] In clinical intravascular ultrasound studies, regression of atherosclerosis in coronary artery disease patients was achieved with injection of apoA-I or its genetic variant apoA-I_{Milano}.[29,30] Furthermore, infusion of a single dose of reconstituted human HDL (rHDL group) versus saline (placebo group) into patients with peripheral artery disease undergoing femoral atherectomies 5 to 7 days later reduced plaque lipid content, vascular cell adhesion molecule 1 expression and macrophage cell size (because of diminished lipid content) compared with the placebo group.[31] These clinical infusion studies are consistent with those in which functional HDL was infused into rabbits or mice.[28,32,33] Thus, to fully interpret the findings of Voight et al, we would need information on the functionality of the HDL particles in the people with the genetic variations under study.

Overall, then, the limited clinical data and the animal studies imply that the beneficial effects of HDL on atherosclerotic plaques are more likely to occur when apoA-I/HDL levels are raised by exogenous injection or stimulation of endogenous production of functional particles. A major caveat, however, is that the ultimate test—an outcome study of the protection from MI by increasing the number of functional HDL particles—has not been conducted. Nonetheless, given the potential benefits, different approaches to increase apoA-I production or the formation of functional HDL particles are in, or are being considered for, development or testing in clinical trials. These include infusion of recombinant apoA-I and apoA-I mimetics, delipidation of HDL followed by reinfusion, and agents that increase the transcription of the apoA-I gene (RVX-208)[34–37] or the hepatic abundance of ABCA-1

(which is required for HDL assembly), such as an inhibitor of microRNA-33.[27,38] Such approaches may give our HDL plumber more tools to use than just a plunger.

In summary, Voight et al have published data consistent with other Mendelian randomization studies, as well as intervention trials, suggesting that raising HDL-C level is not causally related to protection from MI. This is in stark contrast to what observational studies would predict. Although we agree with them that their work challenges the concept that raising of plasma HDL-C level will uniformly translate into reductions in risk of myocardial infarction, based on the information we have reviewed about the complexity of the RCT pathway and HDL functionality, it is premature to cast aside the potential benefits of this fascinating lipoprotein, giving the plumbers the welcome expectation of additional work in a depressed HDL economy.

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