HDL and Cardiovascular Risk
Time to Call the Plumber?
Bernd Hewing, Kathryn J. Moore, Edward A. Fisher

Plasma HDL Cholesterol and Risk of Myocardial Infarction: A Mendelian Randomisation Study
Voight et al

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. However, in a recent study, Voight et al 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. The major approach used was Mendelian randomization, a method developed to infer disease causality of a genetic variation. 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 increased plasma HDL-C 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 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, AIM-HIGH, and dal-OUTCOMES) 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. 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. In a study involving 54,500 individuals from the Copenhagen City Heart Study (CHHS) 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. 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 CHHS population, were not associated with decreased risk of MI. 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...
LDL-C lowering and HDL-C raising,12 a scenario not tested showed that the lipoprotein profile for the best outcome was plaque size determined by intravascular ultrasound, 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 dalceptrapib and a significant lowering effect on LDL-C, also failed to provide benefit, and even showed evidence in the ILLUMINATE4 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.1 However, 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 Lilly) 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 Atero-thrombosis Intervention in Metabolic Syndrome with Low HDL Cholesterol/High Triglyceride and Impact on Global Health Outcomes (AIM-HIGH)1, despite niacin’s effectiveness in reducing cardiovascular events in the HATS3 trial, although this was smaller and of different design. AIM-HIGH has been criticized on a variety of fronts14 giving hope 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-OUTCOMES6 study with the cholesteryl ester transfer protein inhibitor dalceptrapib 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 dalceptrapib 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 dalceptrapib and a significant lowering effect on LDL-C, also failed to provide benefit, and even showed evidence in the ILLUMINATE4 trial of causing excess deaths from cardiovascular and other diseases in the treatment group.

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-OUTCOMES6 study with the cholesteryl ester transfer protein inhibitor dalceptrapib 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 dalceptrapib 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 dalceptrapib and a significant lowering effect on LDL-C, also failed to provide benefit, and even showed evidence in the ILLUMINATE4 trial of causing excess deaths from cardiovascular and other diseases in the treatment group.

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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 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 HDL plumbers the welcome expectation of additional work in a de-pressed HDL economy.

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**Disclosures**

None.

**References**


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