Editorial

Examining the paradox of high high-density lipoprotein and elevated cardiovascular risk

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When high density lipoprotein cholesterol (HDL-C) was identified as a protective factor in atherosclerotic cardiovascular disease (ASCVD), the inverse relationship between HDL-C and ASCVD was thought to be linear (1). However, data from several cohorts has revealed a plateau in the inverse association above roughly 40 mg/dL (2). There is even a suggestion of a U-shaped curve from sub-analyses in large observational studies whereby extremely high HDL-C levels may be related to increased risk (3). However, very few individuals within any single medium-sized cohort under 10,000 participants have extremely elevated HDL-C levels and even fewer with incident events to analyze.

Thus, the recent study of two large population-based cohorts in Denmark (52,268 men and 64,240 women) represents the largest study with the most events among those with extremely elevated HDL-C to directly assess the presence or absence of a U-shaped curve with regard to mortality, cardiovascular, and non-cardiovascular events in a sex-specific manner (4). This study showed that there was a nadir in mortality rates among European Caucasians at HDL-C levels of 73 mg/dL for men and 93 mg/dL for women. All-cause mortality rates increased significantly for men with HDL-C levels above 97 mg/dL and for women above 135 mg/dL, representing 224 and 41 events respectively. Findings were specific to CV mortality but were not significant for mortality related to other causes. Examination of the restricted cubic spline curves confirmed a plateau above 40 mg/dL in both men and women and an upward inflection beyond the respective sex-specific nadir points. Now that the epidemiologic U-shaped pattern of HDL-C and CV risk has been solidified, the big question is why? What are the mechanisms explaining these associations? Possible explanations of high HDL-C include genetic mutations leading to very high HDL-C that also confer adverse CV risk or confounding by factors associated with both mortality and CV risk and high HDL-C levels. Alternatively, extreme elevations in HDL-C may directly represent dysfunctional HDL in some individuals, which may in turn promote CV risk.

Genetic mutations linked to HDL-C levels have played an important role in advancing our knowledge about the role of HDL in cardiovascular disease. Deletions in the gene encoding endothelial lipase (LIPG) result in modest elevations in HDL-C levels due to reduced phospholipolysis (5) but have not been shown to be associated with expected decreased or paradoxically increased risk (6). Loss of function mutations in *SCARB1*, the gene encoding the major transporter allowing circulating HDL to deliver cholesterol back to the liver for excretion, result in marked increases in HDL-C levels and, paradoxically, increased risk of coronary heart disease (7). Mutations in the gene encoding cholesterol ester transfer protein (CETP) result in increased HDL-C levels of varying magnitude and mixed associations with ASCVD (8-10). In one study, the CETP mutation was associated with an increased risk of ischemic heart disease in the female participants only (11).

CETP inhibitors raise HDL-C levels by 60–100% but in large event-driven randomized controlled trials have either increased CV risk (torcetrapib), had no effect (dalcetrapib and evacetrapib), or decreased CV risk (anacetrapib), with the decreased risk likely due to apolipoprotein B-lowering effects and not because of increased HDL-C (12-14). In summary, genetic mutations leading to elevated HDL-C have not consistently been associated with the expected decrease in ASCVD risk and some mutations have been linked to increased risk. These findings confirm that HDL-C levels alone do not adequately reflect the anti-atherogenic or pro-atherogenic potential of HDL and that the HDL hypothesis has shifted from measuring circulating cholesterol levels to deep phenotyping of HDL composition and function to better understand the role of HDL in CV disease.

A key purported anti-atherogenic function of HDL is to promote reverse cholesterol transport (RCT) whereby cholesterol is removed from peripheral tissues and delivered to the liver for excretion into bile and feces out of the body. The ability of apolipoprotein B-depleted plasma or serum to accept cholesterol from lipid laden macrophages (cholesterol efflux) is the initial critical step in RCT and can be measured *ex vivo* in humans (15). Several large observational studies have demonstrated inverse associations between baseline cholesterol efflux capacity and incident ASCVD in both low- and high-risk populations, even after adjusting for HDL levels. Cholesterol efflux not only associates with ASCVD but, unlike HDL-C, also improves ASCVD risk prediction beyond traditional risk factors, coronary calcium, family history and C-reactive protein (16). Thus, HDL-C levels are an insufficient surrogate for cholesterol efflux, a key HDL function. HDL also exerts anti-inflammatory and anti-oxidative functions which can become pro-inflammatory and pro-oxidative in certain settings such as prevalent coronary disease or diabetes (17,18).

Deep phenotyping of metrics of HDL composition such as particle number and size as well as protein concentrations of apolipoprotein A-I offer further insights into HDL metabolism. In IDEAL and EPIC-Norfolk, similar to the U-shaped curve with extreme elevations of HDL-C seen in the Danish study, markedly increased HDL particle size conferred an increased risk of major cardiovascular events, with a relative risk as high as 3.49 in patients with HDL particle sizes upwards of 10.07 nm relative to patients with a HDL particle size less than 8.6 nm (19). This paradoxical relationship between HDL size and cardiovascular risk was attenuated after adjusting for triglyceride levels, small LDL particles and waist to hip ratios. In contrast, there was a consistent protective relationship between high ApoAI levels and cardiovascular events. Similarly, total HDL particle concentration has emerged as a robust, independent risk factor contributing to cardiovascular risk (20-22). Thus, metrics related to HDL particle concentration rather than cholesterol content and size may offer better insights into the role of HDL metabolism and CV disease.

Lastly, apart from pathobiologic explanations of paradoxical relationships between HDL-C and events, residual and reverse confounding must also be addressed. Prior reports of increased mortality among those with elevated HDL-C have been confounded by alcohol intake, which tends to raise HDL-C levels and is linked to cancer and increased all-cause mortality (23-25). In the present study, a continuous measure of self-reported alcohol intake explained 5% of the variance in HDL-C levels, behind only triglyceride levels and body mass index. However, multivariable Cox models included adjustment for alcohol intake and the point estimates for extreme HDL-C levels in models with and without alcohol intake did not differ qualitatively. At least in low-risk European Caucasians, it can be safely concluded that alcohol intake does not explain the U-shaped curve of HDL-C and increased cardiovascular and all-cause mortality. In addition, the investigators performed sensitivity analyses excluding those that died up to 5 years from study entry with no change in the main findings, excluding the possibility of reverse confounding explaining the results.

These concepts raise several important questions when it comes to therapeutic interventions targeting HDL metabolism. Raising HDL-C levels may be too simplistic a therapeutic target if HDL particle composition and function are not taken in to consideration. This has been confirmed in multiple failed trials of interventions that raise HDL-C. The AIM-HIGH and HSP2-THRIVE studies failed to show benefit despite achieving elevation in HDL levels as expected with addition of niacin therapy (26,27). Perhaps the lack of clinical benefit can be explained in part by a lack of improvement in cholesterol efflux capacity or anti-inflammatory properties of HDL despite increase in absolute HDL-C values (28). As described above, CETP inhibitors were studied in large outcomes trials with the first three resulting in either harm or no benefit despite increases in HDL-C as high as 70% (12,13,29). Although CETP inhibitors do increase global cholesterol efflux, the effects are modest and also heterogeneous with respect to transporter-specific efflux (30). In addition, they may adversely

affect other HDL functions on the vasculature (12). The recent REVEAL trial with anacetrapib led to a reduction in CV outcomes but was likely due to its apolipoprotein B-lowering effects and not the elevations in HDL-C. Apo AI has remained a consistent protective factor for cardiovascular disease and small molecule mimetics that raise circulating levels of lipid-poor Apo A-I are being studied in CV outcomes trials (31).

In conclusion, the complexity of HDL biology is inadequately reflected by measurement of HDL-C levels. The future of HDL likely lies in incorporation of deep phenotyping of HDL composition and function for a more sophisticated understanding of cardiovascular risk at an individual and population level. Standardized and uniform classifications of HDL-C levels, particle size, composition and function will be necessary for continued investigations (32). Trials of therapeutics targeting HDL-C levels have shown us that a different approach may be necessary. Therapeutic interventions targeting HDL will likely only be successful at reduction in cardiovascular events if their impact on reverse cholesterol transport and other functions is better understood and thoroughly characterized. HDL continues to play an important protective role in cardiovascular disease. As its many roles are elucidated, we will further our understanding of how to measure and target HDL for cardiovascular disease prevention.

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Footnote

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