

High-density lipoprotein: quantity or quality?

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Chronic kidney disease (CKD) affects approximately 13% of the general population (1). Patients with CKD have increased risk for cardiovascular events (2). Moreover, all-cause mortality is similar in patients with CKD and in those with a history of myocardial infarction (3). The pathogenesis of cardiovascular disease (CVD) in patients with CKD is multifactorial and includes increased oxidative stress, vascular calcification and subclinical inflammation (4).

Serum high-density lipoprotein cholesterol (HDL-C) levels are frequently reduced in patients with CKD (4,5). Moreover, HDL function appears to be impaired in CKD and the atheroprotective properties of HDL diminish as glomerular filtration rate (GFR) declines (4,5). The importance of HDL functionality versus HDL quantity has become apparent in recent years. Several studies showed that serum HDL-C levels only partly determine HDL functionality, particularly cholesterol efflux capacity (6,7). Moreover, HDL functionality appears to be more strongly related to cardiovascular risk than serum HDL-C levels (6,7). In contrast, Mendelian randomization studies showed that single nucleotide polymorphisms that modulate HDL-C levels do not affect the incidence of coronary heart disease (8,9).

In this context, the results of a recent study by Bowe *et al.* are clinically relevant (10). In this study, a cohort of 1,764,986 US veterans were followed for a median of 9.1 years and the association between serum HDL-C levels and all-cause mortality was analyzed. Subjects with HDL-C levels 26–49 mg/dL had lower all-cause mortality than those with HDL-C levels <25 mg/dL. However, this protective effect of HDL-C was attenuated in subjects with HDL-C levels ≥50 mg/dL. Moreover, subjects at the highest decile of HDL-C levels [median 68 mg/dL, interquartile range (IQR) 64–77 mg/dL] had higher all-cause mortality than

those with HDL-C levels at the lowest decile (median 27 mg/dL, IQR 24–28 mg/dL). Therefore, the association of HDL-C and all-cause mortality appeared to follow a U-shaped curve. Moreover, the reduction of all-cause mortality with increasing HDL-C levels was smaller in patients with GFR <45 mL/min/1.73 m², suggesting that the presence of CKD diminishes the protective effects of HDL (10).

The findings of the elegant study by Bowe *et al.* (10) further strengthen the importance of evaluating HDL functionality and the limitations of relying solely on HDL-C levels for mortality risk prediction. Indeed, subjects with the highest HDL-C levels had increased all-cause mortality (10). Preclinical data also suggest that HDL at very high levels might exert detrimental effects, including an impairment of angiogenesis (11). Moreover, randomized clinical trials with agents that increase HDL-C levels did not show a reduction in cardiovascular events (12). Indeed, treatment with niacin had no effect on cardiovascular morbidity in patients with established CVD in the atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) and in the Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) trials (n=3,414 and 25,673, respectively) despite an increase in HDL-C levels by 25 and 14%, respectively (13,14). In addition, treatment with cholesteryl ester transfer protein (CETP) inhibitors also did not prevent cardiovascular events even though these agents substantially raise HDL-C levels. In fact, torcetrapib, the first CETP inhibitor that was evaluated in clinical trials, increased cardiovascular morbidity and all-cause mortality in the Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE)

trial (n=15,067), despite an increase in HDL-C levels by 72% (15). Even though these adverse outcomes were attributed to off-target effects of torcetrapib, namely an increase in blood pressure (16), two newer CETP inhibitors, dalcetrapib and evacetrapib, also failed to affect cardiovascular outcomes in the dal-OUTCOMES trial (n=15,871) and in the Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition With Evacetrapib in Patients at a High Risk for Vascular Outcomes (ACCELERATE) trial (n=12,095), respectively, which were prematurely discontinued for futility (17,18). Notably, dalcetrapib and evacetrapib increased serum HDL-C levels by 29 and 78–88%, respectively (17–19), again suggesting that very high HDL-C levels do not necessarily decrease cardiovascular morbidity. Anacetrapib, another CETP inhibitor, increases HDL-C levels by 138% (20) and its effects on cardiovascular events are currently being evaluated in the Randomized Evaluation of the Effects of Anacetrapib Through Lipid-modification (REVEAL) trial (n=30,624), which is expected to be completed in January 2017 (21).

On the other hand, accumulating data suggest that HDL functionality is mostly independent of serum HDL-C levels and is a better predictor of cardiovascular events than HDL-C concentration (6,7). The findings of the study by Bowe *et al* also point to the same direction. Indeed, HDL was less protective against all-cause mortality in patients with CKD, a condition associated with impaired HDL function (5). However, it should be emphasized that there is currently no universally accepted gold standard for evaluating HDL functionality. It might also be difficult to identify such a method, given the multiple functions of HDL and the uncertainty regarding which one is more strongly related to the antiatherogenic effects of HDL. Moreover, methods used for evaluating cholesterol efflux capacity, possibly one of the most important functions of HDL, are labor-intensive, expensive and available only in specialized centers. Perhaps more importantly, it is unclear whether improving HDL function will translate into reduced cardiovascular and all-cause mortality. Moreover, there are currently no agents that selectively affect HDL functionality, a prerequisite for evaluating the effects of modulating HDL functionality on cardiovascular events.

It should also be mentioned that the study by Bowe *et al*. has several limitations (10). First, only elderly men and predominantly Caucasians were evaluated and it is therefore unclear whether the findings are applicable to younger subjects, women or other ethnic groups. Moreover, HDL-C

levels are affected by smoking, physical activity, alcohol consumption and insulin resistance, which in turn are associated with cardiovascular and all-cause mortality risk, and these parameters were not recorded (10). Of note, the cholesterol efflux capacity of HDL is independent of other traditional cardiovascular risk factors (7), which represents an additional advantage of evaluating HDL functionality rather than quantity.

Despite these limitations, the study by Bowe *et al*. (10) provides additional evidence that measuring HDL-C levels is a suboptimal marker for assessing cardiovascular risk. There is a pressing need to develop inexpensive methods that will accurately gauge the functionality of HDL. The application of such methods in large prospective studies will provide more robust evidence regarding the association between HDL functionality and cardiovascular events. The next and more crucial step will be to evaluate in a randomized controlled trial whether improving HDL functionality will reduce cardiovascular morbidity.

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Footnote

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