Editorial

High density lipoproteins and kidney function: the friend turned foe?

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The crucial role of low density lipoprotein cholesterol (LDL-C) in cardiovascular disease (CVD) and mortality has been extensively demonstrated, and thus reducing LDL-C is one of the key therapeutic approaches for cardiovascular risk reduction (1). However, the exact role of high density lipoproteins (HDL) is still an enigma and as research expands it is getting even more complicated. In this scenario, the work of Bowe and co-workers (2) adds a new piece of this puzzle by demonstrating the existence of a U-shape distribution of the risk of all-cause mortality in relation to HDL-C levels with a reduced risk only in those with intermediate HDL-C levels (between 25 and 50 mg/dL). This relation between HDL-C and all-cause mortality was previously reported, specifically in hemodialysis patients (3). Nevertheless, Bowe *et al*. (2) have investigated patients without a previous history of end-stage renal disease (ESRD), dialysis or kidney transplant, further demonstrating the U-shape association between HDL-C levels and mortality even in the absence of established kidney disease.

In addition, this work further demonstrates that the risk of mortality and its association with HDL-C is modified by the estimated glomerular filtration rate (eGFR) and the presence of CVD. Thus, lower eGFR values attenuate the protective effect of HDL-C and the presence of CVD attenuates the association of HDL-C and all-cause mortality (2). This longitudinal study has two main strengths: it includes a large cohort of patients (1,764,986 men) and a long-term follow-up (median 9.1 years) giving robustness to the obtained results, contrary to other clinical studies reporting inconsistent results due to short term follow-up and small sample size. Thus, the present study further expands the previously reported results (4) pointing out towards a dysfunctional shift in HDL of patients with kidney disease. It is important to highlight that HDL-C levels do not reflect HDL protective properties. In fact, it is already known that HDL protective properties are determined by their quality (i.e., composition and functionality) but not through their quantity in terms of amounts of transported cholesterol (what is measured by HDL-C) (5,6). This has been more evident as therapeutic attempts to raise HDL-C levels have failed to reduce cardiovascular risk (7-9). In this context, the study of Bowe *et al*. (2) affords the intriguing concept of the existence of an U-shape relation between HDL-C and all cause mortality, pointing out once more to the lack of usefulness of analyzing total HDL-C levels as a measure of HDL quality and thus their protective effects. The higher risk seen in the study of Bowe *et al*. (2) in subjects with higher HDL-C levels is in line with the results obtained in clinical trials where CETP inhibitors that significantly increased HDL-C did not reduce the risk of cardiovascular morbidity and mortality (8). Thus, it seems clear that increasing HDL-C levels does not necessarily mean increasing functional HDL.

This discrepancy between HDL-C levels and HDL functionality becomes even more important in the presence of high cardiovascular risk situations such as hypercholesterolemia, diabetes or renal disease in which shifts in HDL lipidic and proteomic distribution could directly affect HDL functionality disrupting the association between HDL-C levels and protection (10,11). Indeed, we have recently demonstrated in an experimental pre-clinical model that HDL from hypercholesterolemic pigs are less protective than those of normocholesterolemic animals against cardiac ischemia/reperfusion injury (12). Additionally, we have found important changes in the HDL proteomic distribution in familial hypercholesterolemia

patients that seem to predispose to cardiovascular event presentation and mortality (10).

The meaning of the U-shape association between HDL-C and mortality reported by Bowe *et al*. (2) has to be taken with caution as the work does not examine the cause of death. Even though, authors report a lower presence of diabetes, hypertension and CVD in those patients with higher HDL-C levels, suggesting that cardiovascular events probably do not explain the higher risk of death in this subgroup of patients. On the other hand, authors observe an increase in the prevalence of cancer and a high percentage of patients with high CRP levels indicative of the presence of infections or a chronic inflammatory state. This observation underscores a potential implication of immune and inflammatory disorders in the increased risk of death in patients with high HDL-C levels. In fact, HDL protein cargo includes inflammation-related proteins (13). It has been shown that patients with ESRD have an increased content of the acute phase protein serum amyloid A1 in their HDL compared to control subjects and that these HDL show an impaired cholesterol efflux ability (14). Nevertheless, the study of Zewinger *et al*. (4) found an increase in both all-cause and cardiovascular mortality in patients with higher HDL-C levels in patients with kidney dysfunction.

The work of Bowe *et al*. (2) shows the influence of eGFR in the relation between HDL-C and mortality. It is important to highlight that the eGFR measurement was performed in patients without a previous history of ESRD, dialysis or kidney transplant, allowing the study of the added value of eGFR in risk assessment and its interaction between HDL-C levels in relation to mortality, even in the absence of established kidney disease.

At this point it would be necessary to investigate to which extent changes in HDL protein composition could be behind the interaction of eGFR with the association between HDL-C and mortality. Indeed, a previous study showed that the association between HDL-C and mortality was only present in patients with normal kidney function (eGFR >90 mL/min) and was lost in patients with mid and advanced kidney dysfunction (eGFR =60–89 mL/min). But when the levels of Apo A–I, main protein component of HDL, were analyzed, the association between HDL-C and mortality was seen in patients with both, normal and mid kidney function, but not in patients with advanced kidney dysfunction (4), supporting the notion that renal diseases in addition to influencing HDL-C levels modify HDL composition and functionality (11,14-16). Furthermore, HDL protein changes in kidney diseases could specifically affect those HDL subclasses with higher atheroprotective properties. Thus, it has been previously reported that the HDL3 subfraction, the one that that exhibits higher atheroprotective properties (17), is decreased with the increase in the severity of chronic kidney disease (CKD) (18). Moreover, it has been proposed that the observed alterations in lipid metabolism in CKD patients could be dependent on the decline in the eGFR (19). This association could be due in part to changes in the metabolism of HDL components. Indeed, CKD has been associated with a diminished lecithin-cholesterol acyltransferase (LCAT) gene expression by the liver reducing its circulating levels and activity (20-22) and directly impacting HDL maturation. Interestingly, LCAT changes, specifically in the HDL3 subfraction, have been found in high risk patients previous to the presentation of a fatal ischemic event (10). In this context, a loss of HDL protective properties could be behind the elevated risk for cardiovascular events and mortality in patients with kidney disease. Indeed, nearly half of all deaths of dialysis patients can be attributed to CVD (23,24). It is noteworthy that the American College of Cardiology/American Heart Association (ACC/AHA) and the European Society of Cardiology (ESC) consider CKD a risk predictor equivalent to the presence of coronary artery disease (25,26).

With all this in mind, it is crucial to uncover the mechanisms by which HDL are modified in kidney disease patients in order to identify new potential therapeutic options that may help to fill in the risk gap left by statins, specially in the context of CKD where a certain resistance to lipid-lowering therapies has been demonstrated (27).

In conclusion, the study of Bowe *et al*. (2) evidences once more the relevance of HDL quality more than HDL-C levels in risk assessment, and the direct impact of risk factors and co-morbidities in HDL-mediated protection. Further research is needed in order to find a tool that can serve as a biomarker of HDL quality, instead of HDL-C levels, that can be used in risk stratification and prognosis, especially in high risk patients.

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Footnote

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