Cardiorenal biomarkers: one step closer

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Comment on: Martens RJ, Kimenai DM, Kooman JP, *et al.* Estimated Glomerular Filtration Rate and Albuminuria Are Associated with Biomarkers of Cardiac Injury in a Population-Based Cohort Study: The Maastricht Study. Clin Chem 2017;63:887-97.

Patients with renal insufficiency have increased risk for cardiovascular disease (CVD) mortality (1), as lower estimated glomerular filtration (eGFR) and greater albuminuria are both independently associated with higher risk of coronary heart disease and heart failure (2). Therefore, the link between chronic kidney disease (CKD) and CVD underscores the need to identify and utilize cardiac biomarkers to assist in diagnosis of CVD and profiling of CVD risks among CKD patients, especially in the acute setting. However, levels of cardiac biomarkers such as cardiac troponin (cTn) T and I, and N-terminal pro-brain natriuretic-peptide (NT-proBNP), are well known to be increased among patients with poor renal function but without known CVD (3,4). This rise in biomarker levels might be partly attributable to decreased clearance of these markers in the kidney, as well as to minor myocardial necrosis or left ventricular hypertrophy (5). Hence, interpretation of a change in those cardiac biomarkers in CKD patients might be challenging, although cTnT and NT-pro-BNP apparently retain their ability to predict cardiac disease among CKD patients (6,7). Understanding the association between kidney injury and cardiac biomarkers may help clinicians manage patients with greater accuracy.

A recent study by Martens *et al.* took on an important task and examined the cross-sectional associations of eGFR and urinary albumin excretion (UAE) with high-sensitivity (hs) cTnT, hs-cTnI, and NT-proBNP in 3,103 individuals from the Maastricht Study, a population-based diabetes-enriched cohort study (8). In this study, populations with different stages of CKD or with normal kidney function

were investigated, and the association of eGFR with cardiac biomarkers was found to become already apparent in patients with borderline-normal level of eGFR. Levels of eGFR 60–90 mL·min^{-1}·(1.732)$^{-1}$ or <60 mL·min^{-1}·(1.732)$^{-1}$ were both associated with elevated levels of hs-cTnT, hs-cTnI and NT-pro-BNP compared to levels of eGFR >90 mL·min^{-1}·(1.732)$^{-1}$ after adjustments for age, sex, and ischemic ECG abnormalities. With a fall in eGFR by 10 mL·min^{-1}·(1.732)$^{-1}$, hs-cTnT, hs-cTnI and NT-pro-BNP rose by about 10%. These observations stress the need to consider cardiovascular risk and outcomes among subjects with eGFR of 60–90 mL·min^{-1}·(1.732)$^{-1}$, who have been sparsely reported, because the propensity for CVD may increase within the population with early renal dysfunction. A plausible explanation of this association, as suggested by Martens *et al.*, could be microvascular disease as a systemic condition and a potential common mechanism influencing in parallel both the kidney and heart in CKD (8). In support this notion, our previous study showed that patients with very mild renal insufficiently already exhibited attenuated coronary flow reserve (9).

Definition of CKD stage 2 requires kidney damage over 3 months with mildly decreased GFR. However, the authors did not fully clarify whether the participants with eGFR of 60–90 mL·min^{-1}·(1.732)$^{-1}$ had renal pathological abnormalities or markers of kidney damage. Therefore, this group may in fact include subject both with and without CKD, complicating the interpretation of the association of mild renal insufficiency with cardiac injury. Furthermore, it is important to note that 43% of the participants in the Maastricht Study had impaired glucose metabolism, and they

may thus not faithfully represent the general generation. An additional caveat is that glomerular hyperfiltration, defined as a GFR of >125–140 mL·min^{-1}·(1.732)$^{-1}$, reflects an early stage of diabetic nephropathy, and is also associated with an increase in incident albuminuria in the general nondiabetic population (10). Thus, the control group with eGFR >90 mL·min^{-1}·(1.732)$^{-1}$ in this diabetes-enriched cohort might have included participants with early kidney injury, again complicating the ability to use the group with high eGFR as healthy controls. Stratifying this population also by CKD stages may help resolve this question.

The association of kidney function with cardiac biomarkers also underscores the need to interpret levels of cardiac biomarkers based on different level of eGFR, in agreement with KDIGO guidelines (11). One of the limitations for this interpretation is that current reference values of hs-cTnT, hs-cTnI and NT-pro-BNP are based on levels in healthy individuals, thus baseline measurements of hs-cTnT and cTnI show poor diagnostic accuracy among patients with renal insufficiency (12,13). Few studies attempted to define optimal cutoff levels of cardiac biomarkers for diagnosis of CVD in CKD individuals. Yang *et al.* reported the cutoff-value of hs-cTnT for diagnosis of acute myocardial infarction of 99.55 ng/L in CKD stage 3, 129.45 ng/L in CKD stage 4, 105.50 ng/L in CKD stage 5, and 149.35 ng/L in dialysis patients in China (14). For NT-pro-BNP, DeFilippi *et al.* suggested that no further GFR-based adjustment was required for diagnosis of decompensated heart failure in CKD patients (15). Contrarily, Jafri *et al.* reported that optimal NT-pro-BNP cutoffs for systolic heart failure diagnosis throughout the CKD spectrum were 4,502 pg/mL (16). Overall, the need is stressed for further studies on optimal cutoff-value of hs-cTn and NT-proBNP levels or meaningful value change of cardiac biomarkers in different stages of CKD.

Incidentally, the associations of categorical and continuous eGFR with hs-cTnT in the study by Martens *et al.* were slightly stronger than those with hs-cTnI (8). It indicates that renal function might be less important for cTnI clearance compared with cTnT, possibly due to greater susceptibility of cTnT in uremia, leading to accumulating smaller cTnT fragments (17) with relatively free passage through the glomerular filtration barrier. Interestingly, a recent study showed that hs-cTnI was superior to hs-cTnT in detecting coronary artery disease among CKD patients (18), possibly because hs-cTnT is more dependent on renal elimination. Conversely, hs-cTnT outperformed hs-cTnI in predicting all-cause mortality in

CKD patients (19). Therefore, priority should be placed on the specific goal when selecting a biomarker in clinical practice.

Importantly Martens *et al.* also addressed the association between UAE and cardiac markers. UAE ≥30 mg/24 h was associated with higher hs-cTnT, hs-cTnI and NT-pro-BNP, and UAE 15–30 mg/24 h was associated with higher hs-cTnI compared with UAE <15 mg/24 h, after adjustment for demographic information. Hence, patients with microalbuminuria or albuminuria had higher levels of cardiac biomarkers, in line with a previous study (20). Both renal and myocardial ischemia may be partly explained by underlying microvascular dysfunction, which is prevalent among CKD patients and patients with coronary artery disease (21), and can cause albumin leakage through the glomerular capillary wall, as well as troponin T release from cardiomyocytes (22). In addition, microvascular dysfunction can lead to subclinical myocardial ischemia manifested by increased cTn release (8). Moreover, the authors found that the association between albuminuria and NT-pro-BNP was stronger in individuals with type 2 diabetes mellitus. Diabetic patients with high degree of albuminuria often have volume-load causing left ventricular hypertrophy (23), which may increase NT-pro-BNP in CKD patients (24). Data on left ventricular size could have been useful in the study by Martens *et al.*

Since the study by Martens *et al.* is cross-sectional, no data of cardiovascular and renal outcomes were recorded. Such data would have enabled comparisons of the significance of the interactions among eGFR, albuminuria and cardiac biomarkers, which may help to develop strategies for CVD risk stratification and its prevention. Incidentally, while eGFR and albuminuria predict cardiovascular outcomes, cTnT and NT-proBNP concentrations are conversely independently predict end renal stage disease risk (25).

Indeed, Martens *et al.* brought us closer to the understanding that these biomarkers may need to be considered as 'cardiorenal biomarkers' rather than merely cardiac markers. Besides cTnT, cTnI and NT-pro-BNP, additional emerging 'cardiorenal biomarkers' may include Fibroblast Growth Factor-23, Growth Differentiation Factor-15, and Copeptin, which may help explore pathologic mechanisms linking heart and kidney. Further development in this field and greater understanding of the role of 'cardiorenal biomarkers' with CKD and CVD, alone or in combination, may help to improve clinical managements of patients.

Footnote

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