The well-known association between chronic kidney disease (CKD) and cardiovascular disease (CVD) is usually attributed to the loss of renal function, as estimated by the glomerular filtration rate (GFR). Currently, a decreased GFR is considered to be one of the most important parameters indicating an unfavorable cardiovascular risk profile in patients with heart failure (HF). In the past 2 decades, however, urinary albumin excretion (UAE) has gained considerable attention. Studies have shown that 30–40% of patients with chronic HF have either microalbuminuria (MA; defined as a urinary albumin-to-creatinine ratio [UACR] of 30–299 mg/g) or macroalbuminuria (defined as UACR >300 mg/g). MA is associated with other risk factors that themselves might be causal or linked with causal processes, it is also an independent predictor of future strokes, myocardial infarction, and death. In addition, MA can predict future HF. Over the past 2 decades, a growing number of epidemiology studies have reported a link between MA and HF (Figure).

Despite its increasing recognition as a CVD risk factor, the definition of MA is based on its ability to deduce diabetic nephropathy, with the aim of determining the level of albuminuria that predicts progression to heavy proteinuria. The predictive value of MA for diabetic nephropathy is now accepted universally. The traditional upper normal limit of the UACR has been 30 mg/g, although recent epidemiological data suggest that the average UACR in the general population is actually much lower. Furthermore, in the range below the current MA threshold, an elevated UACR is associated with increased CV events and death in patients with preserved (>60 ml·min⁻¹·1.73 m⁻²) or mildly reduced (30–59.9 ml·min⁻¹·1.73 m⁻²) eGFR. Moreover, low-grade albuminuria below the current MA threshold is linked unambiguously to an increased CVD risk in HF patients. The postulated downward shift in the pathophysiology of albuminuria in HF compared with that in other diseases suggests that the contribution of various pathophysiological factors to albuminuria in HF differs from that in other diseases. Also in the CHARM and ALOFT studies,¹ the protective response to an angiotensin-receptor blocker or renin inhibitor in HF patients is smaller than that in diabetic nephropathy patients.

GFR and albuminuria are 2 different entities physiologically; each is an independent predictor of CVD events and all-cause mortality, although they often coexist. Unlike previous reports,¹,³ Miura et al found that the predictive value of subclinical MA for future CVD events was limited to a preserved or mildly reduced eGFR. Above all, in HF patients with a mildly reduced eGFR, subclinical MA had a prognostic impact comparable to that of MA and macroalbuminuria, in which subclinical MA should be interpreted as a threshold cutoff value, rather than as a continuum. Moreover, there was no significant association between subclinical MA and CVD outcome in patients with a marked loss in renal function (eGFR <30 ml·min⁻¹·1.73 m⁻²). Therefore, the sensitivity of UACR for predicting future CVD events in HF patients seems to be higher during the early stage of CKD vs. the later stage. These interesting findings are reminders of the fact that albuminuria is used primarily to screen and identify patients with early kidney disease, and that the increased risk is caused by albuminuria as a reflection of vascular disease, rather than by GFR as a reflection of renal function. Nevertheless, when considering the importance of early detection of CVD risk, the multifactorial pathogenesis of HF, and cardiovascular multimorbidity in HF patients (coexisting CVD and CKD), it is noteworthy that subclinical MA can predict CVD outcomes in HF patients.
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with normal and early stage CKD. Early evaluation of the UACR would be advantageous for early prediction of CVD events in HF patients.

Although albuminuria reflects widespread vascular damage and might be a sign of systemic vasculature dysfunction, the biological mechanisms underlying the relationship between albuminuria and CVD risk have not been elucidated completely. Clearly, a very low UAE concentration is unlikely to be a direct cause. Albuminuria develops in association with many extrarenal processes, which probably encompass multiple mechanisms, including vascular injury, systemic and glomerular hypertension, and inflammation, resulting in either impairment of the glomerular filtration barrier integrity or tubular reabsorption of albumin as a consequence of tubular damage. Because of the underlying biological complexity of albuminuria, it may reflect various pathological conditions in the vasculature. HF develops via various underlying mechanisms involving extracardiac and cardiac pathologies, so a single biomarker might not reflect all facets of HF. Combining albuminuria with other biomarkers from different pathophysiological processes, such as natriuretic peptides, cardiac troponin T, and soluble ST2, ultimately might enable better risk stratification for predicting HF prognosis by integrating multiple features of HF.

This downward resetting of normal UACR levels raises questions regarding how to interpret subclinical MA detected in a spot sample. Subclinical MA can also be a response to physiological stressors, such as exercise and posture. In addition, it remains unclear whether fluctuations in the UACR around the subclinical MA range during follow-up are associated with the prognosis of HF patients. Further studies using serial UACR measurements are needed to clarify these points. Moreover, the association between subclinical MA and the risk of CVD events raises interesting questions on how to manage subclinical MA detected in HF patients. As shown here, the fact that small differences between subclinical MA and MA can lead to different HF prognoses implies the need for subsequent intervention for UAE in HF patients. A recent meta-analysis of 32 randomized studies enrolling hypertensive or diabetic patients showed that a successfully reduced UAE is associated with a reduced risk of CVD and mortality. In HF patients, however, a favorable risk outcome achieved by reducing UAE (at least within the subclinical MA range) has not yet been demonstrated. If these findings are validated, HF patients with subclinical MA could be targeted for preventive strategies, and screening based on the UACR would enable clinicians to provide early interventions. Conversely, is risk reduction achieved only in HF patients with higher baseline values? Future studies should explore whether subclinical MA is just a HF risk marker or rather a modifiable risk factor. Because albuminuria is an easily measured and relatively inexpensive marker, albuminuria-targeted therapy is an attractive subject for future research on the therapeutic strategies for treating HF.

Disclosures

None.

References