Systemic Inflammation Is a Key Factor for Mortality Risk Stratification in Chronic Kidney Disease Patients With Coronary Artery Calcification

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Coronary artery calcification (CAC) has been associated with myocardial ischemia, coronary arterial vasodilatory dysfunction, coronary artery disease (CAD), and all-cause mortality. Increases in the CAC score (CACS) are not consistent with those in the conventional coronary risk score, namely, the Framingham risk score, which considers age, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, treatment for hypertension, and cigarette smoking. However, risk prediction of all-cause mortality by CACS is superior to that by the Framingham risk score. The CACS value was reported as a better risk predictor for cardiovascular disease than the value of multiple biomarkers, including high-sensitivity C reactive protein (hs-CRP), interleukin-6, myeloperoxidase, B-type natriuretic peptide, and plasminogen activator-1 in asymptomatic participants without known CAD. The addition of CAC, but not biomarkers, has been reported to result in superior risk reclassification for future cardiovascular events to that by the Framingham risk score. When a comparison of hs-CRP vs. CAC for risk prediction was performed in JUPITER-eligible participants, the presence of CAC was found to predict the risk of CAD over a markedly wider range than hs-CRP >2 mg/dl. When hs-CRP and CAC were evaluated simultaneously for risk predictions of non-fatal myocardial infarction and coronary death, the relative risk for patients with the highest quartile hs-CRP (>4.05 mg/L) and highest tertile CACS (>142.1)
was 6.1-fold greater than that for patients with lower hs-CRP (<4.05 mg/L) and the lowest tertile CACS (<3.7). The combination of factors/scores, including CAC, hs-CRP, conventional risk scores, and other markers, that provides the best predictive value for the incidence of CAD and mortality has been the focus of a number of studies.

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Chronic kidney disease (CKD) is one of the greatest risk conditions associated with progression of CAD. CAC has been reported to progress through hyperphosphatemia, increases in the calcium-phosphate product, vitamin D therapy, the administration of a vitamin K inhibitor (warfarin), reductions in Klotho, and increases in fibroblast growth factor 23 (Figure: blue lines). The progression of CAC has been identified as an independent predictor of cardiovascular outcomes in CKD patients. However, because CAC is prevalent, particularly in CKD patients, a large number of CKD patients with CAC do not have myocardial ischemia or CAD. Thus, a new risk stratification system is needed for CKD patients with CAC.

In this issue of the Journal, Hwang et al investigate renal function and systemic inflammation in an evaluation of the relationship between CACS and mortality in a large-scale cohort of patients referred for CAC measurement. They followed 30,703 consecutive individuals who underwent CAC measurements for a median of 79 months and subsequently identified 3 main issues. The prevalence and extent of CAC were greater in individuals with lower estimated glomerular filtration rate (eGFR) and the highest hs-CRP (Figure: red lines ①). Furthermore, a lower eGFR was strongly associated with a higher CACS, and this relationship was stronger in patients with higher hs-CRP levels (Figure: red line ②). In addition, a greater CAC burden was associated with high mortality in CKD patients only in those with higher hs-CRP levels (Figure: red line ③). These findings indicate that the measurement of hs-CRP has the potential to stratify the risk for all-cause death in CKD patients with CAC.

One of the challenges for the future is to clarify the mechanisms responsible for the increased risk of all-cause death because of progression of CAC among only those CKD patients with slightly enhanced systemic inflammation. Elucidation of the underlying mechanisms may lead to the development of preventive therapy based on risk stratification of CKD patients with CAC. Another challenge for the future is to examine whether preventive therapy based on risk stratification using hs-CRP measurements leads to better clinical outcomes. Coronary angiography is required to confirm a diagnosis of CAD. The incidence of contrast-induced nephropathy after coronary angiography is higher in patients with CKD than in those with normal kidney function. Reduced renal function and proteinuria have been identified as independent risk factors for contrast-induced nephropathy. Thus, a safe stratification system that preserves renal function is needed to achieve better clinical outcomes for CKD patients with CAC.

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