Cystatin C in a High-Risk Combination

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Community studies demonstrate a rising prevalence of cardiovascular (CV) disease with declining renal function. The risk of subsequent CV events is higher among patients with chronic kidney disease (CKD) than among those with normal renal function. However, limited information exists on the risks associated with lesser degrees of CKD in patients with CV diseases. Cystatin C is a novel endogenous marker of renal function that might be more sensitive for detecting mild to moderate decrements in glomerular filtration rates (GFR). It is a member of the family of cystein proteinase inhibitors that is produced at a constant rate by all nucleated cells. It is freely filtered across the glomerular membrane and completely catabolized in the proximal tubules. Most studies suggest that it is not affected by age, sex, or muscle mass, and has the superior diagnostic accuracy compared with serum creatinine for early renal impairment and for predicting all-cause mortality, CV events, and heart failure (HF). However, there is still a paucity of evidence that it actually leverages important clinical decisions more effectively than the use of serum creatinine alone or eGFR.

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Improvements in the treatment of acute myocardial infarction (AMI), especially use of reperfusion therapy, have led to large numbers of survivors. However, the incidence of secondary cardiac events including recurrent myocardial infarction is unchanged. Also, there has been concern that an increasing pool of survivors might affect the incidence of HF after AMI. Recently, Velagaleti et al reported an increase in the incidence of HF in recent decades that paralleled the decrease in mortality after MI in the Framingham cohorts. The estimated incidence of post-MI HF is varying from 10% to 40% and it is associated with a markedly elevated risk of death. Therefore, early risk stratification is still necessary in the management of the patients with AMI.

In this issue of the Circulation Journal, Ichimoto et al provided evidence for the prognostic value of cystatin C in patients with ST-elevation MI (STEMI). Seventy-one patients with STEMI were divided into 2 groups according to the cystatin C level measured before emergent percutaneous coronary intervention. Although there were no significant differences in baseline characteristics, except for the serum creatinine level between the groups, the group with the higher cystatin C level showed a worse event-free survival during the mean follow up of 5.6 months by Kaplan–Meier analysis. Also, cystatin C was an independent predictor of CV events by the Cox proportional-hazards model. The authors concluded that cystatin C might be associated with higher CV events, mainly due to hospitalization for HF, in patients with STEMI. These findings are consistent with a previous report by Jernberg et al, which evaluated the prognostic value of cystatin C in patients with symptoms suggestive of a non-ST-elevation acute coronary syndrome (ACS) and compared it with that of creatinine and other biochemical indicators of increased risk. Ix et al and Koenig et al recently demonstrated that higher cystatin C concentrations are associated with mortality, CV events, and incident HF, independent of traditional CV risk factors, among ambulatory patients with coronary heart disease (CHD). Thus, in addition to ACS and CHD, Ichimoto et al have added to the literature on the utility of cystatin C for the prediction of CV events in patients with STEMI.

Several issues should be noted to interpret the present findings. The sample size was so small that any negative findings could be caused by a low statistical power. In particular, it remains uncertain whether cystatin C measurement is really superior to serum creatinine alone or eGFR for predicting the events after STEMI, and whether cystatin C is a predictive marker only for incident HF or also for CV death, reinfarction, or revascularization. Further studies with a larger number of patients will clarify these questions. Renal disease might not only be identified by low GFR but also by the presence of abnormal quantities of albumin in the urine. In fact, the appearance of pathological albuminuria often precedes the functional deterioration that is evidenced by a decline in GFR. The link between albuminuria and adverse CV events has been widely recognized in general populations, patients with diabetes or hypertension, and people at high risk for CV disease. Recently, Berton et al reported urinary albumin excretion measured by the albumin-to-creatinine ratio improved clinical prediction over baseline traditional multivariable risk models in AMI patients. The relationship between albuminuria and serum cystatin C level might be intriguing in this clinical setting. The other issue is that although the association of cystatin C with CV events is presumably caused by its correlation with GFR, there might exist the possibility that circulating cystatin C either have directly harmful effects or reflect another pathologic process distinct from renal function. Indeed, lower plasma levels of cystatin C were previously reported in patients with an aortic aneurysm and AMI. Knight et al reported that cystatin C was signifi-

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cantly associated with C-reactive protein, smoking and body mass index, even after adjustment for creatinine clearance in the general population.14

The present study emphasizes the importance of considering renal function in early evaluation of patients with STEMI. When considering that the incidence of post-MI HF might be increasing, the measurement of cystatin C in STEMI will be useful in clinical practice. It might also suggest that AMI patients with mild to moderate renal dysfunction should receive such aggressive treatments as early revascularization and long-term β-blockers and ACE inhibitors.15 Although AMI and renal dysfunction have been known as a high-risk combination previously, we should now have a new understanding of the relationship through cystatin C measurement.

References


