Is Cystatin C the Answer to Detecting Progression in CKD?

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Although increasing interest is given to early detection of chronic kidney disease (CKD), there is controversy over whether all patients need our attention. It has been argued, for example, that many patients with stage 3 or 4 CKD, especially the elderly, are not at increased risk for mortality and progression. Peralta et al., in this issue of JASN shed new light on this question. They studied the Multi-Ethnic Study of Atherosclerosis (MESA) and Cardiovascular Health Study (CHS) data sets to determine whether risk prediction for stages 3 and 4 CKD improves by measuring estimated GFR (eGFR) calculated with not only the creatinine Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation but also the cystatin C CKD-EPI equation. They show that risk for progression in patients with stage 3 CKD on the basis of the level of creatinine eGFR is not increased when cystatin C eGFR is ≥60 ml/min per 1.73 m². Only in 50% of the cases in which cystatin C eGFR is also decreased is the risk for mortality, cardiovascular events, and heart failure elevated significantly. In addition, the risk for ESRD is only 2.6-fold elevated in patients with creatinine eGFR <60 ml/min per 1.73 m² and normal cystatin C eGFR, whereas it is 23.8-fold elevated in cases in which cystatin C eGFR is also decreased. The additive value of cystatin C eGFR is also independent of albuminuria. Some issues should be considered in interpreting these findings.

First, why in this study does creatinine CKD-EPI eGFR not discriminate for increased vascular and mortality risk? The use of the creatinine CKD-EPI equation has been shown to result in reclassification of 30 to 40% of patients identified by the creatinine-based Modification of Diet in Renal Disease (MDRD) equation as having an eGFR between 30 and 60 ml/min per 1.73 m² compared with a group with an eGFR between 90 and 120 ml/min per 1.73 m².2,3 Similarly, in the Australian Diabetes, Obesity and Lifestyle (AusDiab) study, the adjusted hazards for all-cause mortality were 1.26 and 2.30 for the creatinine CKD-EPI eGFR groups 45 to 59 and 30 to 45 ml/min per 1.73 m², respectively, compared with the group without CKD. These data seem contradictory to those in the current report from Peralta et al., in which patients with a creatinine CKD-EPI eGFR of <60 ml/min per 1.73 m² do not have an increased mortality risk.

Several reasons may explain the seemingly contradictory findings, such as differences in cohort characteristics, for example, age, or in the choice of the reference category. With respect to age, it is important to note that the average age in the MESA and CHS cohorts (62 and 72 years, respectively) is higher than in the ARIC and AusDiab cohorts (54 and 52 years, respectively). Recent data suggested that the association between lower eGFR and mortality risk is less steep in elderly than in younger patients.4–6 With respect to the importance of the chosen reference category, in the AusDiab study, the group without CKD was the reference, suggesting that patients with elevated albuminuria were excluded. Thus, the reference in the AusDiab study is a lower risk group than in the study by Peralta et al.7 that included patients with elevated albuminuria. Moreover, because there is a J-shaped association between creatinine eGFR and mortality, it might well be that the choice of Peralta et al. as a reference group with an eGFR of >60 ml/min per 1.73 m² results in a less steep risk prediction for patients with an eGFR of <60 ml/min per 1.73 m² than when a reference group with a smaller eGFR range (90 to 120 ml/min per 1.73 m²) is chosen, as in the ARIC study.

Second, although cystatin C eGFR associates well with outcome and perhaps better than creatinine eGFR, this does not necessarily suggest that cystatin C eGFR is a good proxy for true GFR. Unfortunately, only a few well-powered studies have investigated the association of cystatin C eGFR with iothalamate or inulin clearance in the general population.7 Why, then, may cystatin C eGFR predict risk better than creatinine eGFR in general population studies? Recent studies suggested that cystatin C is elevated, independent of renal function, in patients who smoke5 or have obesity5–10 low-grade systemic inflammation,8,11 or mild hyperthyroidism.12 All of these factors are independent predictors for adverse outcomes. Peralta et al.1 adjust for most of these covariates, which makes their conclusions robust; that is, cystatin C may have a role in identifying patients who have CKD and have the highest risk for complications.

Third, Peralta et al.1 limit their study to patients with a
creatinine eGFR of <60 ml/min per 1.73 m². They advise first to measure creatinine eGFR and, when it is <60 ml/min per 1.73 m², next to measure a cystatin eGFR. By this approach, however, they will miss the approximately 5% of the population with some form of albuminuria and a creatinine eGFR of >60 ml/min per 1.73 m². These patients with stages 1 and 2 CKD have a risk that is equal to or even greater than the risk for patients with a creatinine eGFR between 45 and 60 ml/min per 1.73 m² and normal-range albuminuria, with respect to both mortality and kidney outcomes. Peralta et al. correctly state, therefore, that “as the presence of albuminuria can also detect CKD subjects who are at high risk for adverse events, even in the range of an eGFR >60 ml/min per 1.73 m², future studies should focus on evaluating the cost-effectiveness of a triple screen of renal markers to include albuminuria, serum creatinine, and cystatin C measurements.”

With respect to cost-effectiveness, we recently showed that screening for albuminuria by delivering a first morning urine void to a central laboratory, followed by a complete renal and vascular workup only of patients with an albuminuria concentration >10 mg/L and the subsequent start of angiotensin-converting enzyme inhibition in patients in whom micro- or macroalbuminuria is confirmed, costs $37,000 per life-year gained in the overall population that was screened and $18,000 if screening was limited to the population aged >50 years. Moreover, such an albuminuria-targeted approach was better in differentiating patients with increased risk for cardiovascular events and progressive loss of eGFR from those without increased risk when compared with screening approaches that primarily screen for impaired creatinine eGFR. Cost-effectiveness analyses for screening cystatin C eGFR to identify high-risk patients with CKD have not yet been performed. The data by Peralta et al., together with previous findings of this research group that cystatin C adds to risk prediction independent of albuminuria in patients with a creatinine eGFR of >60 ml/min per 1.73 m² may warrant such cost-effectiveness analyses.

DISCLOSURES
None.

REFERENCES