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Cystatin C, Creatinine, and Albuminuria: Bringing Risk Into 3 Dimensions

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It has become well recognized that elevated levels of serum cystatin C confer an increased risk of cardiovascular disease (CVD) events and all-cause mortality, outperforming creatinine-based estimates of glomerular filtration rate (GFR) in this regard in several studies.^{1,2} Cystatin C also has been associated with incident heart failure,³ correlated with the severity of New York Heart Association heart failure functional class,⁴ and in patients with CVD, elevated cystatin C level repeatedly has been shown to be a marker of poor prognosis,^{5–7} even in those with creatinine-based estimated GFR (eGFR_{cr}) >60 mL/min/1.73 m². A major advance has been the availability of equations to estimate GFR from cystatin C (eGFR_{cys}), with the suggestion that a mild decrease in eGFR_{cys} is a more robust prognostic marker for CVD events than eGFR_{cr}. The major shortcoming of the initial studies of cystatin C was that urine measurements were not available to assess the presence and degree of albuminuria, a factor that repeatedly has been shown to associate independently with CVD events and mortality in those with and without decreased eGFR_{cr}.^{8–10} Without concomitant measurements of cystatin C and albuminuria, it was conceivable that the association of cystatin C with CVD events and mortality might have been confounded by albuminuria.

However, recently, a series of further studies in cohorts with all 3 measurements has begun to elucidate the respective roles of cystatin C, creatinine, and albuminuria. These studies have described the independent associations of albuminuria and elevated cystatin C level with CVD risk and mortality in several different patient populations. Choi et al¹¹ showed that decreased eGFR_{cys} and albuminuria were associated independently with a nearly 2-fold increase in mortality in individuals infected with human immunodeficiency virus (HIV). Menon et al² showed that in patients with chronic kidney disease (CKD), cystatin C level correlated strongly with all-cause and CVD mortality and was comparable, if not superior, to serum creatinine level and measured GFR using iothalamate, even after adjustment for proteinuria. Finally, similar findings were noted in older adults in a large Swedish cohort¹² and in the Cardiovascular Health Study (CHS) cohort for both patients with diabetes¹³ and the general population.¹⁴

The study by Waheed et al¹⁵ featured in this issue of the *American Journal of Kidney Diseases* extends those findings by showing the utility of eGFR_{cys} and albuminuria as

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prognostic markers in a broad sample of the adult population from the Atherosclerosis Risk in Communities (ARIC) cohort, a population-based cohort of middle-aged individuals from several US communities. The investigators used the CKD Epidemiology Collaboration (CKD-EPI) cystatin C level, age, sex, and race equation,¹⁶ as re-expressed for standardized cystatin C assays.¹⁷ Participants were categorized based on $eGFR_{cys}$ and spot urine albumin-creatinine ratio and were followed up for the composite outcome of CVD events, incident heart failure, and all-cause mortality for a median of 10.2 years. Like the CHS, the ARIC cohort included both white and African American participants, whereas participants in the CHS had a mean age of 78 years and the mean age for ARIC participants was nearly 15 years younger.

Waheed et al¹⁵ again have shown that lower $eGFR_{cys}$ is associated with increased CVD risk, incident heart failure, and mortality; however, the authors further expand our knowledge in this area by exploring the relationship between $eGFR_{cys}$ and albuminuria in the context of their associations with CVD and mortality risk. They demonstrate a strong, independent, and graded risk of the composite outcome in those with higher albuminuria, as well as with lower $eGFR_{cys}$. Furthermore, even in those with $eGFR_{cys}$ of 60–74 mL/min/1.73 m² with no albuminuria (albumin-creatinine ratio <10 mg/g), they found a 28% increased risk of the composite outcome, providing further evidence for the claim that a mild decrease in $eGFR_{cys}$ may provide valuable prognostic information.

Clearly, an abundance of evidence already exists supporting the potential prognostic importance of cystatin C level, and the study by Waheed et al¹⁵ suggests that $eGFR_{cys}$ and albuminuria each provide independent refinement of risk stratification. In this cohort, once again, the increased risk associated with lower $eGFR_{cys}$ was more linear than that associated with lower $eGFR_{cr}$ computed using the CKD-EPI creatinine equation. In addition to its increased sensitivity for risk associated with decreased $eGFR$, cystatin C level has potential benefits as a filtration marker in comparison to creatinine.¹⁸ Some evidence suggests that cystatin C level is affected less by variations in age, sex, and ethnicity, which probably is related to less dependence on muscle mass, and thus $eGFR_{cys}$ may be more accurate than $eGFR_{cr}$ in people with chronic diseases or malnutrition that affects muscle.¹⁹ However, cystatin C is not without its limitations. Its level may be affected by nonrenal factors, including thyroid dysfunction and corticosteroid use,²⁰ and its variation in states of acute illness is yet to be fully described. Furthermore, the cost of measuring cystatin C may be up to 10 times²¹ that of serum creatinine, and the present lack of standardization of commercially available assays may in aggregate be contributing to the hesitation to adopt this new method.

The robust finding that cystatin C level and albumin-uria provide independent risk information lays further groundwork for the concept recently proposed by Peralta et al²² of a “triple marker” approach for CKD evaluation, with supporting data from several large cohorts.²³ Using such an approach in the REGARDS (Reasons for Geographic and Racial Differences in Stroke) cohort of adults older than 45 years, these investigators found the highest risk of death in those with CKD defined by all 3 measures (albuminuria, $eGFR_{cys}$, and $eGFR_{cr}$). They also found that the presence of CKD as defined by both $eGFR_{cys}$ and $eGFR_{cr}$ conferred a much greater risk of progression to end-stage renal disease than either

marker alone. This approach would take advantage of the ubiquity of serum creatinine and urine albumin measurements and use serum cystatin C level to refine the risk associated with these 2 measures.

Taken together, the work of Waheed et al¹⁵ and Peralta et al^{22,23} brings us closer to establishing a framework for the most efficacious use of cystatin C level in routine clinical practice. Instead of retaining our present “2-dimensional” approach to the diagnosis and staging of CKD using albuminuria and eGFR_{cr} or debating the merits of an either-or approach to eGFR_{cys} and eGFR_{cr}, perhaps we should move toward a 3-dimensional method using all 3 markers in appropriately selected patients. The details of such an approach, deciding in what order to offer these tests and describing the clinical scenarios in which each assay would be appropriate, are of great importance because the additional testing could prove costly. The caveat to sequential testing (ie, starting with eGFR_{cr} and albuminuria and refining findings with eGFR_{cys}) that is raised by the study from Waheed et al¹⁵ is that we may miss an important subset of the general population at increased risk of adverse events. This is confirmed by the finding of increased risk of the composite outcome of death, incident heart failure, and CVD in nonalbuminuric patients with eGFR_{cys} of 60–74 mL/min/1.73 m². Given that 2,018 of the total 10,403 ARIC Study participants (19%) used in the analysis were in this category and mean eGFR_{cr} in this subset was 78.4 mL/min/1.73 m², we estimate that >10% of the total study population are at increased risk based solely on an abnormal eGFR_{cys}, a group that clinically would remain unrecognized with the current standard of eGFR_{cr} and albuminuria testing alone. However, even if we routinely identified these individuals, it is not clear what we would offer them in the clinic. The follow-up care for individuals identified by such an approach then would have to be determined because interventions for the cardiovascular risk associated with nascent kidney disease are not yet defined. However, we clearly are moving toward a clinical role for cystatin C, one in which the use of 3 complementary tests may bring our understanding of kidney disease risk into sharper focus.

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