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See related article, "Podocin Inactivation in Mature Kidneys Causes Focal Segmental Glomerulosclerosis and Nephrotic Syndrome," on pages 2181–2189.

## More Evidence that Cystatin C Predicts Mortality Better than Creatinine

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The main clinical benefit of estimating renal function in the general population is to identify and treat patients at risk for

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developing ESRD, cardiovascular events, and death.<sup>1</sup> Unfortunately, the most widely used equations to estimate GFR are limited, in part, by their reliance on serum creatinine as the filtration marker (estimated GFR [eGFR]). The Modification of Diet in Renal Disease (MDRD) equation, for example, overestimates renal function among individuals with low muscle mass and underestimates it among those with GFR >60 ml/min per 1.73 m<sup>2</sup>.<sup>2–4</sup> The use of serum cystatin C, a cysteine protease inhibitor that is freely filtered by the glomerulus, has potential advantages over creatinine as a filtration marker in that its production is not dependent on muscle mass.<sup>2</sup> As a result, cystatin C offers opportunities to estimate GFR more accurately than creatinine-based equations and additionally may predict worsening kidney function even when the GFR is actually near the normal range.<sup>5</sup>

Beyond the relationship to measured GFR, cystatin-C–derived eGFR (ecGFR) was a better predictor of mortality than creatinine-based estimates in a study of elderly individuals<sup>6</sup>; however, the ability to generalize these findings to a younger and broader set of individuals is unknown. In this issue of *JASN*, Astor *et al.*<sup>7</sup> extend previous observations and demonstrate convincingly that ecGFR predicts mortality more accurately than the MDRD equation in a sample from the general population in the United States. If replicated, then these findings should spur trials to determine whether the use of cystatin C improves patient outcomes by identifying those with an elevated risk for death, both within and outside the setting of diagnosed chronic kidney disease (CKD).

Astor *et al.*<sup>7</sup> focus on the relationship of ecGFR to mortality, but it is instructive to examine the challenges of using creatinine-based equations to assess renal function—the original reason for interest in cystatin C as a diagnostic test. The accuracy of a creatinine-derived eGFR and its value for detecting progressive kidney disease depends on the patient's level of renal function and associated level of proteinuria.<sup>1</sup> Patients with an eGFR <30 ml/min per 1.73 m<sup>2</sup> using MDRD are at substantial risk for later developing ESRD, but among patients with less severely diminished eGFR (45 to 90 ml/min per 1.73 m<sup>2</sup>), the prognostic value of an eGFR is limited, particularly when albuminuria is absent. For instance, follow-up of individuals who participated in the Multiple Risk Factor Intervention Trial (MRFIT) revealed that a subset with eGFR <60 (mean 55 ml/min per 1.73 m<sup>2</sup>) have only a 5.6% absolute risk for ESRD over 25 yr. In comparison, among participants with eGFR 60 to 75 ml/min per 1.73 m<sup>2</sup>, approximately 5.7% of those with 1+ proteinuria on urine dipstick evaluation and 17.7% of those with 2+ proteinuria develop ESRD.<sup>8</sup> The creatinine-based eGFR alone, therefore, has limited utility in predicting which patients with mildly diminished eGFR and no proteinuria will experience renal deterioration in the future.<sup>9</sup>

There are theoretical reasons to believe that cystatin C is a superior filtration marker compared with creatinine,<sup>10</sup> however, a comparison by Stevens *et al.*<sup>11</sup> of the performance characteristics of the MDRD equation with a cystatin C–based estimate in a large pooled population of patients with established

CKD revealed that cystatin C offers only modest improvement in accuracy. The performance of cystatin C–based measures to estimate renal function in the general population or among those with mild reductions in kidney function has not been explored fully.

Although eGFR derived from creatinine is also thought to be an important risk factor for mortality,<sup>12</sup> previous studies indicated cystatin C may be a powerful predictor of death independent of creatinine. In a cohort of 4637 community-dwelling elderly patients, Shlipak *et al.*<sup>6</sup> demonstrated a J-shaped relationship between the eGFR using the MDRD equation and mortality: Diminishing eGFR was associated with a graded increase in the risk for death, with this relationship reversing direction at higher levels of renal function such that patients with eGFR >74 ml/min per 1.73 m<sup>2</sup> had a higher (albeit NS) adjusted rate of mortality compared with patients with an eGFR from 66 to 74 ml/min per 1.73 m<sup>2</sup>. Without an apparent biologic basis for the relationship between greater renal function and a greater rate of death, this J-shaped relationship has been explained by the overestimation of renal function by creatinine-based equations among patients with more comorbidities and muscle wasting. By contrast, in the same cohort, diminishing ecGFR showed a monotonic relationship to mortality across all strata of renal function. Notably, this relationship is evident even in the absence of data on urinary protein excretion.<sup>6</sup>

Astor *et al.*<sup>7</sup> assembled a cohort of patients from the general population using the Third National Health Examination Survey (NHANES) to evaluate the risk of death associated with lower levels of eGFR estimated from cystatin C, from serum creatinine, or from both. Compared with previous published reports, the strengths of this work include median follow-up of 8 yr, inclusion of patients with ethnic diversity, a wide age range, and analytical rigor with particular focus on the implications of cystatin C among patients with eGFR >60 ml/min per 1.73 m<sup>2</sup> as calculated using the MDRD equation. Similar to the study by Shlipak *et al.*,<sup>6</sup> the results by Astor *et al.*<sup>7</sup> show an inverse and generally monotonic relationship between ecGFR and mortality, whereas the estimated filtration rates derived from MDRD and from cystatin and creatinine had more J-shaped relationships to all-cause mortality (Figure 1 in the accompanying article<sup>7</sup>).

Lower ecGFR is also informative in predicting mortality, in particular in the range in which creatinine-based eGFR underestimates renal function and is prone to misclassifying patients as having stage 3 CKD according to the Kidney Disease Outcomes Quality Initiative (KDOQI) staging system.<sup>13</sup> Among patients classified by the MDRD equation as having eGFR 30 to 59 or eGFR 60 to 89 ml/min per 1.73 m<sup>2</sup>, overall mortality is significantly elevated only when cystatin C also categorizes patients as having an ecGFR <60 ml/min per 1.73 m<sup>2</sup>; therefore, cystatin C is able to stratify patients with respect to the risk for death even among those with mild or even no reduction in renal function as assessed by a creatinine-based equation.

Astor *et al.*<sup>7</sup> also address the question of whether serum

cystatin C should be used alone or in combination with creatinine to determine patients who are at risk for adverse health events. Previous studies that examined the performance characteristics of the MDRD and other equations, such as the pooled analysis of patients with CKD by Stevens *et al.*,<sup>11</sup> found the combination of creatinine and cystatin C perform best in estimating measured GFR. In contrast, the receiver operating characteristic curves presented by Astor *et al.*<sup>7</sup> reveal that estimated filtration rates derived from the combination of cystatin C and creatinine levels is actually *worse* at predicting death compared with cystatin C alone. Potential explanations for the divergence of cystatin C from creatinine with respect to predicting death include the possibility that cystatin C is affected by systemic inflammation or other pathophysiologic pathways that amplify the mortality risk independent of GFR.<sup>14,15</sup> A second possibility is that limitations of creatinine as a filtration marker (particularly when GFR is mildly diminished) stand in the way of attempts to elucidate relationships between renal function and mortality that cystatin C–based measures alone can reveal.

Astor *et al.*<sup>7</sup> have strengthened the evidence linking cystatin C to mortality risk, but more work is required before cystatin C can be integrated into clinical practice. First, we need studies showing whether using cystatin C adds value in predicting risk for progression from CKD to ESRD. Given that most patients with CKD die before needing renal replacement therapy,<sup>12</sup> it is possible that risk factors for death differ from risk factors for further loss of renal function. New analyses of cystatin C and renal events should, like this study by Astor *et al.*,<sup>7</sup> also focus on the general population with inclusion of patients with GFR >60 ml/min per 1.73 m<sup>2</sup>. Second, future studies that relate cystatin C to mortality and renal deterioration should ideally be informed by data on proteinuria. Third, to justify bringing cystatin C to routine clinical care, trials showing that the use of cystatin C leads to better selection of patients for treatments that reduce morbidity and mortality in CKD must be performed.

Astor *et al.*<sup>7</sup> confirm that ecGFR is strongly associated with subsequent mortality in a large community-based population. Cystatin C holds promise as a prognostic marker that could eventually be incorporated into existing measures that risk-stratify patients for cardiovascular events or death. Additional careful research, like the study by Astor *et al.*,<sup>7</sup> is needed to clarify whether the association between cystatin C and mortality is mediated by renal function alone. Although further studies are required, Astor *et al.*<sup>7</sup> have moved us closer to sorting out the complex set of relationships among contemporary filtration markers, progressive kidney disease, and mortality risk.

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## DISCLOSURES

None.

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See related article, “Method of Glomerular Filtration Rate Estimation Affects Prediction of Mortality Risk,” on pages 2214–2222.

## Warfarin and Stroke Outcomes in Hemodialysis Patients with Atrial Fibrillation

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The prevalence of atrial fibrillation in ESRD is extremely high, reaching 27%,<sup>1</sup> and fibrillation, as in the general population, also is associated with increased mortality in hemodialysis patients.<sup>2</sup> A large number of trials show the usefulness of oral anticoagulation therapy<sup>1</sup> for primary and secondary prevention of stroke in patient populations with atrial fibrillation absent ESRD.<sup>3</sup> Recently, a large study demonstrated the superiority of oral anticoagulation therapy compared with the combination of clopidogrel plus aspirin with regard to stroke prevention, with no added risk of bleeding.<sup>4</sup> Even trials performed in patients with high hemorrhagic risk who took warfarin, particularly the elderly, show that benefits of treatment exceed the risks when the international normalized ratio (INR) is monitored correctly.

The decision to use oral anticoagulation therapy, particularly warfarin, in patients with atrial fibrillation involves weighing the risk of a thromboembolic event without therapy, or with inadequate anticoagulation, against the risk of a hemorrhagic event on therapy, particularly over-anticoagulation. Efficacy and safety of anticoagulation in atrial fibrillation depend on maintaining the INR between 2 and 3,<sup>5</sup> as recommended by most practice guidelines.<sup>6</sup> Recently an INR of 3.0 to 3.4 has been proposed to achieve optimal anticoagulation intensity in patients with atrial fibrillation.<sup>7</sup> However, dialysis populations are different from the general population.

The association between renal dysfunction and bleeding has long been recognized, even as long as 200 yr ago,<sup>8</sup> and morbidity and mortality from bleeding remain a significant clinical problem in ESRD. Impaired platelet function is one of the main determinants of uremic bleeding. This impairment is multifactorial and includes defects that are intrinsic to platelets and abnormal platelet–endothelial interactions. Uremic toxins and anemia also play a role.<sup>9</sup> Moreover, hemodialysis patients, unlike other patient settings, are exposed to continuous

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