EDITORIAL

Estimated GFR and Risk of Death — Is Cystatin C Useful?

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Current estimates suggest that as many as one in six persons in North America have chronic kidney disease,[1] a condition that may worsen over time and signal the need for continuous monitoring. Knowing which patient with chronic kidney disease is at risk for end-stage kidney disease or death could tell us who needs intensive monitoring or intervention.

The glomerular filtration rate (GFR), the classic measure of kidney function, describes the amount of plasma that is cleared of an endogenous or exogenous marker filtered by the glomeruli per unit of time. Direct measurement of endogenous clearance is difficult, since it requires the timed collection of urine specimens and concomitant blood tests in which an endogenous marker, such as creatinine, is measured. In the measurement of the clearance of an exogenous substance that is infused intravenously, it is necessary to measure the substance in blood and urine samples after a steady-state level is reached, to calculate a disappearance curve from serial blood samples after the substance is injected, or to measure blood and infusate levels. Thus, direct measurement of the GFR is time-consuming, labor-intensive, and costly.

As an alternative, various methods for estimating the GFR have been developed.[2-5] The National Kidney Disease Education Program has recommended the use of the estimated GFR (eGFR) rather than measurement of serum creatinine alone. Until recently, estimating methods were based on serum creatinine as a marker of kidney function. However, because creatinine is also affected by diet, muscle mass or breakdown, and tubular secretion, it is not ideal, and a variety of estimating equations have been used. Recently, cystatin C, a nonglycosylated protein consisting of 120 amino acid residues encoded by *CST3*, has gained traction as an alternative marker.[6] Cystatin C is synthesized and secreted at a nearly constant rate by virtually all nucleated cells. Given its 13-kDa size, cystatin C is freely filtered by the glomeruli. In contrast to creatinine, cystatin C is not excreted in the urine but, rather, is metabolized by the proximal tubule, so timed urine collections are not needed. Cystatin C is particularly useful for estimating kidney function when creatinine production is variable or unpredictable. In some patients (e.g., those with muscle-wasting or chronic disease, elderly persons, women, or vegetarians), the serum creatinine level may be low, yet the true GFR is impaired. In contrast, in other patients, the serum creatinine level may be high, but the true GFR is normal (e.g., in patients with African ancestry, a muscular body habitus, or a high-protein diet).

Two key advances have improved the understanding of cystatin C as a biomarker in kidney disease.[7] First, international laboratory reference standards for cystatin C now exist, which is important when multiple laboratories are performing tests. Second, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) has developed accurate GFR-estimating equations, specifically the 2012 CKD-EPI cystatin C equation and the 2012 CKD-EPI creatinine–cystatin C equation. The development of these equations represents an advance over the 2009 CKD-EPI creatinine equation, which itself is more precise than the equation used in the Modification of Diet in Renal Disease study, especially at increased GFRs. With such equations, it is now possible to compare the classification and utility of equations by each method of calculating the eGFR.

In this issue of the *Journal*, Shlipak et al.[8] describe a meta-analysis of individual-patient data

from 11 general-population studies and 5 studies involving patients with chronic kidney disease to compare current eGFR techniques and their associations with rates of death, death from cardiovascular causes, and end-stage renal disease. Their results suggest that the cystatin C–based calculation of the eGFR confers some benefits by reclassifying 42% of the study participants with a creatinine-based eGFR of 45 to 59 ml per minute per 1.73 m², most of them to less worrisome states of kidney disease. Such a reclassification provided greater accuracy for predicting outcome and would no doubt reassure participants who were reclassified as having less serious or no renal disease. Only 14% of the participants with a creatinine-based eGFR of 60 to 89 ml per minute per 1.73 m² were classified as having worse disease by the measurement of cystatin C.

The participants in the studies reviewed by Shlipak et al. were mainly white or black. Thus, the results cannot be applied to Asian or Hispanic patients except by extrapolation. Furthermore, only 9% of the patients in the study cohort with chronic kidney disease had diabetes, an important limitation of the study. In addition, information is still needed about the use of cystatin C during pregnancy, after renal transplantation, and in pediatric patients.

Incorporating the results of Shlipak et al. into practice requires access to laboratories that routinely measure cystatin C (as compared with international standards) and the calculation of the cystatin C–based eGFR with the use of the 2012 CKD-EPI cystatin C equation. Guidelines for the treatment of chronic kidney disease that were prepared by the working group of the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) foundation recommend the use of cystatin C–based eGFR in patients with kidney-function ranges in which the creatinine-based eGFR has reduced accuracy.[9,10] The guidelines suggest the measurement of cystatin C in patients with a creatinine-based eGFR of 45 to 60 ml per minute per 1.73 m² of body-surface area but who do not have other manifestations of chronic kidney disease, such as microalbuminuria. The increased use of cystatin C evaluation in such patients, and the current findings of Shlipak et al., will probably push clinical laboratories to incorporate this kidney biomarker. Future studies will be needed to define the role of cystatin C in patients with a creatinine-based eGFR of 60 to 74 ml per minute per 1.73 m² who do not have other manifestations of chronic kidney disease but have coexisting illnesses, such as diabetes, congestive heart failure, or hypertension.

Why does the technique for determining the eGFR matter? In the study by Shlipak et al., the 42% of persons with a creatinine-based eGFR of 45 to 59 ml per minute per 1.73 m² who had a cystatin C–based eGFR of more than 60 ml per minute per 1.73 m² had a relative reduction of 34% in the risk of death from any cause, as compared with persons in whom the eGFR was not reclassified. This is important because previous prognostic studies that addressed mortality typically included an increased number of elderly participants with chronic diseases that render the creatinine-based eGFR less reliable than the cystatin C–based eGFR. Therefore, the study by Shlipak et al. effectively shows that the cystatin C–based eGFR offers the best means of predicting rates of death and end-stage renal disease across diverse populations.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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DOI: 10.1056/NEJMe1308505