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Improved Early Risk Stratification with Cystatin C-based eGFR

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Determination of glomerular filtration rate (GFR) is important in detecting kidney disease, monitoring its progression and making treatment decisions. Equations to estimate GFR (eGFR) that include the routinely obtained variables serum creatinine, age, sex, and race are widely used as a practical, low cost tradeoff for the more laborious measurement of GFR (mGFR) by infusion of special markers and measurement of their clearance from plasma or urine. Serum creatinine based estimates of GFR (eGFR_{cr}) nevertheless have a number of important limitations, including confounding by muscle mass, tubular secretion, and extrarenal elimination of creatinine. Reliability of eGFR_{cr} is particularly poor in individuals with hyperfiltration [1, 2], those who follow certain dietary habits, individuals with unusual or unpredictable changes in muscle mass or extremes of weight (e.g., BMI <20 kg/m²), or those who are pregnant [3–5].

In contrast, serum cystatin C may better fulfill important characteristics of an ideal marker of GFR. Cystatin C is an endogenous low molecular mass protein that is produced at a constant rate and nearly completely cleared from the circulation by glomerular filtration with subsequent proximal tubular uptake and catabolism. Hence, cystatin C may be more sensitive and specific than eGFR_{cr} for detecting early changes in kidney function [6, 7], and it improves precision of GFR estimation when used in combination with creatinine (eGFR_{cr-cys}), particularly in persons with impaired kidney function [5, 8, 9]. Although current GFR estimating equations are biased in certain settings and imprecise in all, regardless of the filtration marker used, they still have considerable value as predictors of clinical outcomes. Shlipak and colleagues from the Chronic Kidney Disease Prognosis Consortium recently examined risk classification for all-cause mortality, cardiovascular mortality, and end-stage renal disease (ESRD) according to levels of eGFR using estimating equations based on creatinine, cystatin C, or the combination of these markers in a meta-analysis of 16 international cohorts [10].

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WHAT DOES THIS IMPORTANT STUDY SHOW?

Pooled data from 11 general population cohorts and 5 chronic kidney disease (CKD) cohorts were analyzed. The 90,750 general population participants had preserved kidney function (mean eGFR 84–85 ml/min/1.73 m², depending on the eGFR calculation used) and the 2,960 CKD participants had reduced kidney function of diverse etiologies (mean eGFR 38–39 ml/min/1.73 m²). In the general population, 13.6% of participants died during a mean follow-up of 7.7 years. The adjusted risk of death from any cause was higher for individuals with eGFRs below the reference point of 95 ml/min/1.73 m², with a significance threshold (i.e., the point at which the risk was significantly higher than the risk at the reference point) of 88 ml/min/1.73 m² for eGFR_{cys}, 83 ml/min/1.73 m² for eGFR_{cr-cys}, and 59 ml/min/1.73 m² for eGFR_{cr}, respectively. The relationship between baseline eGFR_{cys} and risk of death was monotonic, whereas the relationships between baseline eGFR_{cr} or eGFR_{cr-cys} and risk of death were J-shaped, such that there was slightly higher risk at the highest eGFR levels. Similar relationships were found in the CKD cohorts.

Among the 64,010 general population participants in whom deaths from cardiovascular disease were ascertained, 5% died from this cause during a mean follow-up of 8.8 years. The risk for cardiovascular deaths became significant below thresholds similar to those for all-cause mortality: 86 ml/min/1.73 m² for eGFR_{cys}, 83 ml/min/1.73 m² for eGFR_{cr-cys}, and 69 ml/min/1.73 m² for eGFR_{cr}; all three equations had a monotonic association with cardiovascular mortality.

Incident ESRD occurred in 357 of 37,872 general population participants and in 1,297 of 2,955 CKD participants during a mean follow-up of 9.3 years. The risk associations for this outcome were similar for all measures of eGFR in both the general population and CKD cohorts and were generally monotonic.

Importantly, across all eGFR categories, when cystatin C was used instead of creatinine as the filtration marker in the estimating equation, reclassification to a lower eGFR was associated with an increased risk of all three outcomes, and reclassification to a higher eGFR was generally associated with a reduced risk of these outcomes. The authors concluded that cystatin C, which is not as confounded by non-GFR determinants as creatinine, improves the prediction power of eGFR for death and to a lesser extent for cardiovascular death and ESRD by reclassifying many participants to different and perhaps more appropriate categories of kidney disease.

HOW DOES THIS STUDY COMPARE WITH PRIOR STUDIES?

The associations between eGFR and health outcomes have been systematically explored in previous analyses [11]. A series of meta-analyses indicated that serum creatinine-based eGFR level predicts all-cause and cardiovascular mortality, acute kidney injury, and CKD progression in general population and high-risk cohorts independently of albuminuria and other cardiovascular risk factors [11–13]. In keeping with the present study, the hazard ratios for ESRD increased exponentially below an eGFR_{cr} of 60 ml/min/1.73m², the associations of eGFR_{cr} with kidney outcomes were stronger than with mortality, and a higher all-cause

mortality was found consistently above 105 ml/min/1.73 m² [11, 14–16], resulting in J-shaped associations. The non-linear relationship with mortality is generally assumed to reflect eGFRcr overestimation of measured GFR in individuals with reduced muscle mass, inflammation, or with morbid conditions unrelated to kidney disease [10, 11, 17, 18]. Previous population-based studies that used serum cystatin C or cystatin C-based equations as predictors of health outcomes [19–22] also found strong and monotonic associations with all-cause mortality and cardiovascular events at eGFR < 60 mL/min/1.73 m². Although cystatin C concentration is not as influenced by factors confounding the association of eGFRcr with health outcomes, it is not an entirely inert filtration marker, as it inhibits endogenous or exogenous cysteine peptidases, modulates the immune system, has antibacterial and antiviral functions, and is produced in response to brain injury [23]. As such, cystatin C is regulated by tissue specific factors, possibly inflammatory and metabolic, that are not related to GFR, but that could influence progression of nephropathy or atherosclerotic vascular disease and improve cystatin's ability to discriminate the risk for ESRD or cardiovascular events in persons with preserved kidney function. This additional information could explain the monotonic relationship observed between eGFRcys concentration and mortality, as opposed to the J-shaped relationships seen for eGFRcr [24].

Only a small proportion of the population in the present meta-analysis (16% of the general population and 9% of the CKD population) had diabetes, the most frequent single cause of kidney failure. Nonetheless, other studies in persons with type 1 or type 2 diabetes and a wide range of eGFR values found similar associations with ESRD and mortality. In Pima Indians with type 2 diabetes and evidence of kidney damage, defined by an ACR ≥ 30 mg/g, but with normal or high-normal kidney function at baseline (average iothalamate measured GFR 136 ± 42 mL/min/1.73 m²), cystatin C was more strongly associated with progression to ESRD than either serum creatinine or mGFR [19]. Cystatin C and eGFRcys had a monotonic relationship with incidence of ESRD, whereas the relationships between mGFR, serum creatinine, or eGFRcr (whether MDRD or CKD-EPI) and ESRD were J-shaped. Similarly, a study involving three cohorts of Caucasian patients with diabetes (364 with type 1 diabetes and ACR ≥ 300 mg/g and 402 with type 2 diabetes from the Joslin clinic, and 399 patients with type 1 diabetes and ACR ≥ 300 mg/g from the FinnDiane study) and baseline eGFRcr < 30 mL/min/1.73 m² found that risk discrimination for ESRD and all-cause mortality was improved by GFR staging with eGFRcys [25]. Although eGFRcr-cys was a more precise estimate of mGFR, it was less predictive of important health outcomes than eGFRcys [8].

WHAT SHOULD CLINICIANS AND RESEARCHERS DO?

Serum creatinine has been used for the last century as a marker of kidney function. Standardization to isotope dilution mass spectrometry (IDMS) in 2005 greatly improved comparability of measurements across laboratories, and it remains the least expensive kidney filtration marker. Although the agreement between eGFRcr and mGFR is imprecise [2, 26], nephrologists generally concur that determining the exact GFR rarely matters [27]. For these reasons, creatinine is used universally as a screening tool for kidney function, and most clinical laboratories automatically report eGFR based on the measured serum creatinine concentration. Regardless of underlying disease, the Kidney Disease Improving

Global Outcomes (KDIGO) guidelines recommend measurements of both eGFRcr and albuminuria for the diagnosis and classification of CKD, reflecting the additive prognostic significance of albuminuria to eGFR [28]. The guidelines further suggest measuring cystatin C to confirm the diagnosis of CKD in patients with eGFRcr of 45–60 mL/min/1.73 m² but without other signs of kidney damage [28]. This recommendation is based on the enhanced accuracy of GFR estimation provided by cystatin C. The study by Shlipak and colleagues also illustrates the enhanced risk stratification for health outcomes of CKD provided by this measure.

Early identification of patients at high risk for CKD and appropriate risk stratification for the adverse health outcomes that accompany CKD may provide an opportunity for tailored therapeutic intervention that could meaningfully slow disease progression and reduce the frequency of these adverse health events. Successful risk stratification may depend more on the ability of a particular marker, including a filtration marker, to identify those at greatest risk for an adverse health event than on its ability to precisely estimate glomerular function. Indeed, cystatin C may enhance the predictive value for important health outcomes more through its non-GFR determinants than by improving the accuracy of the GFR estimate [19, 25]. What these non-GFR determinants are and how they relate to health outcomes remain to be determined. Nevertheless, Shlipak and colleagues have effectively illustrated the clinical value of relating filtration markers to the health outcomes most likely to adversely affect those in whom the markers are measured.

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