Chronic kidney disease (CKD) is recognized as a major global public health problem (1). CKD affects 10% to 16% of the adult population in Asia, Australia, Europe, and North America and is associated with an increased risk for all-cause mortality and cardiovascular disease across both general and high-risk populations (2). Patients in earlier stages of CKD can be detected through laboratory testing using serum creatinine measurements, with effective treatments available for slowing the progression to kidney failure and reducing cardiovascular events. Although the current staging system (3), based largely on estimated GFR (eGFR) or the presence of kidney damage defined by proteinuria or abnormal renal imaging, is clinically useful for classifying patients in different levels of kidney function, it classifies approximately 26 million US adults as having CKD—too many to target for intervention (4). Therefore, methods for identifying the subset of patients who are at the highest risk for adverse outcomes for targeted assessment and interventions would be extremely useful for clinicians. Assessment and consideration of the rate of change in kidney function over time may provide a new avenue and opportunity for identifying individuals at higher risk for adverse outcomes.

In this issue of CJASN, Perkins et al. (5) report the impact of rate of eGFR decline on mortality among adults patients with a diagnosis of stages 3a, 3b, and 4 CKD. The cohort included patients receiving primary care through a large integrated health care system, Geisinger Medical Center, in central Pennsylvania between January 1, 2004, and December 31, 2009. The authors analyzed the data of 15,465 patients for whom the annualized rate of change in eGFR (calculated using the CKD-EPI equation) was estimated. Patients were categorized by tertile of rate of change corresponding to declining (lower tertile), stable (middle tertile), and increasing (upper tertile) eGFR trends over time. The median (interquartile range) change in eGFR in the declining, stable, and increasing groups was \(-4.8 (-8.2 to -3.2)\), \(-0.6 (-1.4 to 0.0)\), and \(3.5 (1.9 to 6.7) \text{ml/min per 1.73 m}^2/\text{year}\), respectively. Cut points for tertiles were \(-2.2 \text{and} 0.8 \text{ml/min per 1.73 m}^2/\text{year}\). The primary outcome was the risk for all-cause mortality for declining and increasing eGFR, in comparison with stable eGFR, over a median follow-up of 3.4 years. The median number of measurements (interquartile range) for the declining, stable, and increasing eGFR categories were 10 (6 to 17), 11 (7 to 17), and 8 (5 to 14), respectively. In the cohort, 41.3% of the population had an eGFR that increased over time. Relative to the stable group, patients with declining eGFR were more likely to be male and older and have diabetes, coronary artery disease, and proteinuria and less likely to have hypertension or hyperlipidemia. In comparison with the stable group, patients with increasing eGFR were more likely to be female and younger and less likely to have diabetes, hypertension, coronary artery disease, and hyperlipidemia. In multivariate adjusted Cox proportional hazards models examining mortality risk, both decreasing and increasing eGFR were independently associated with death relative to those in the stable group. In comparison with patients with stable eGFR, declining eGFR was associated with an 84% increase in the mortality risk, and increasing eGFR was associated with a 42% increased risk. In a spline analysis, a U-shaped relation between rate of change in eGFR and mortality was observed.

The report by Perkins et al. (5) is interesting because it demonstrates that change in eGFR over time, both declining and increasing, is associated with an increased risk for death compared with stable kidney function, suggesting that change in kidney function in general may be an important prognostic marker. Few other general population–based studies (6–10) have reported the relation between the change in eGFR over time and adverse outcomes. Although a universal definition for quantifying rapid loss of kidney function is not available, these studies have consistently demonstrated that decreasing eGFR is associated with higher risk for adverse outcomes.

Perkins et al. (5) determined rate of eGFR change over time using the slope of the eGFR versus time curve. Previous studies estimated rate of change in kidney function using various methods, including annualized rate of change and percentage annual change (4–10). The difference in methods applied and categories used to define change affects the ability to compare results accurately across studies. Consis-
tency in methods to define change in eGFR in future studies would benefit research in this area.

In addition to being one of the largest cohorts exploring the decline in kidney function and risk for future mortality, Perkins et al. (5) captured the group of patients with increasing eGFR over time. A striking observation is the excess mortality risk for patients with increasing kidney function. Results from the Veteran Affairs study by Ai-Al Aly et al. (6) and from the Atherosclerosis Risk in Communities study by Matsushita et al. (8) showed similar patterns with both declining and increasing eGFR associated with increased risk for adverse outcomes, although the results for increasing eGFR did not achieve statistical significance. Although the study by Perkins et al. raises an important observation about the relationship between change in eGFR over time and risk for adverse outcomes, it also raises more questions than it answers, in particular the mechanism to explain an improvement in kidney function over time. Although nutritional status and previous episodes of acute kidney injury were adjusted for in the analysis, the potential for residual confounding remains. The association between increasing eGFR and mortality likely are a consequence of lower serum creatinine generation as a result of reduced muscle mass associated with chronic illness, particularly in the older population, which may not be captured by measures of nutritional status. Furthermore, the authors were unable to control for other potential confounders, including BP control and changes in volume status, which may affect eGFR change over time. Finally, the statistical phenomenon of regression to the mean may have influenced the results obtained, in which extreme serum creatinine results trend toward the mean with repeated measurement, giving an appearance of improvement in eGFR over time. The Chronic Renal Insufficiency Cohort (CRIC), which is obtaining serial measurements of $^{125}$I-iothalamate clearances among one third of its cohort participants (11), will provide important information regarding actual GFR and potential for improvement over time to shed light on this somewhat surprising phenomenon.

Despite these limitations, the study by Perkins et al. (5) highlights the potential impact of changes in eGFR over time. Further studies in this area are required, in particular to determine whether the risk associated with decreasing and increasing eGFR exists across all levels of kidney function, as well as whether the risk is modified by presence and severity of proteinuria. The answers to these questions are of importance because the ability to follow and interpret the rate of change in kidney function has significant implications for identifying patients who require closer monitoring to potentially reduce the risk for adverse outcomes.

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Disclosures
None.

References

See related article, “GFR Decline and Mortality Risk among Patients with Chronic Kidney Disease,” on pages 1879–1886.