Kidney Medicine

Interpreting Estimated GFR Variability and Its Clinical Significance

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"Is there no cause for primary, or spontaneous variability [in natural selection]? Is it not presumed under the law of inheritance that, in order that the offspring may be the exact type of the parent form, all the conditions of generation and life, and all the forces that affect life, whether generating or external, must be precisely the same? Strictly speaking, under the varying circumstances of life, this is never the case; hence slight individual variations; for no individual force can operate as a cause without its effect. These caused variations may sometimes be wide, and may be helpful or hurtful; if helpful, "Natural Selection" would take them up and preserve them and improve them." A. J. WARNER Marietta, Ohio, March 14, 1872; reproduced with permission[1]

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Whether genetic, physiologic, or pathologic, heterogeneity is common in medicine and sheds important light on the cause and prognosis of many disease states. Some variability in physiologic processes, such as nocturnal dipping of blood pressure, neurohormonal release, and respiratory sinus variation appear beneficial,[2-4] but others seem to lack advantages. For example, higher blood pressure variability over time is associated with risk of myocardial infarction, stroke, and mortality.[5] In contrast, reduced heart rate variability is associated with increased risk of new cardiac events.[6] Serum creatinine levels and its derivative, estimated glomerular filtration rate (eGFR), are often assessed repeatedly to monitor kidney disease progression in clinical practice, and thus, eGFR variability of varying degrees is commonly observed. eGFR is affected by several physiologic and environmental stimuli, including changes in renal plasma flow because of initiation or titration of many medications, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and nonsteroidal anti-inflammatory drugs; intensification of antihypertensive therapy; and volume depletion. eGFR variability may also reflect alteration in kidney regulatory mechanisms because of reduced renal reserve or nephron mass or vascular disease within renal arteries. Because of its frequent observation in clinical practice, there has been growing interest in relating variability in eGFR with clinical outcomes. Greater variability in eGFR has been proposed as a dynamic surrogate marker of reduced kidney resilience.[7] Consistent with this, prior studies have demonstrated that greater eGFR variability associates with new or worsening kidney disease and higher risk of dialysis, cardiovascular disease events, and all-cause mortality.[7,8,9]

In this issue of *Kidney Medicine*, Fravel et al[10] add important new insights to the evidence linking eGFR variability with subsequent clinical outcomes. The investigators performed a post hoc analysis of the ASPirin in Reducing Events in the Elderly trial.[11] The study assessed daily low dose aspirin in healthy older adults, testing an intervention that does not meaningfully affect kidney function. During nearly 3 years of follow-up, and with more than 800 composite death/dementia/physical disability events as well as nearly 400 cardiovascular disease events, the investigators found strong associations of eGFR variability over 2 years with these outcomes. The associations were robust in individuals with and without chronic kidney disease as well as across a number of thoughtful sensitivity analyses evaluating different methods to assess eGFR variability.

This study has several strengths and provides several new insights relative to prior studies on eGFR variability. It benefits from a large sample size, protocol-driven measurements of eGFR at specified time points, availability of measurements of multiple key confounders, and adjudication of clinical end points. The authors also considered different methods to assess variability and found consistent results. Importantly, the investigators extend the findings to a population of generally healthy older adults, whereas most prior studies have investigated populations with prevalent chronic kidney disease, cardiovascular disease, or high risk of these conditions.[8,9,12] However, some limitations must also be considered while interpreting this new study. Most notably, eGFR variability was computed using only 3 eGFR data points that were each 12 months apart, so the prognostic value of shorter-term eGFR variability remains uncertain. With that said, the results are generally similar to prior studies that used shorter timeframes between eGFR assessments.[12] The eGFR variability metric should truly reflect eGFR fluctuations and to accomplish this, Fravel et al[10] fit a mixed linear effect model and evaluated the standard deviation of the model residuals, but it was derived from a mean eGFR value and thus may not account for individual visit-to-visit fluctuations.

In summary, the elegant study by Fravel et al[10] provides yet another study demonstrating the strong association of eGFR variability with clinical outcomes and extends findings to generally healthy elders and to key age-related end points, including disability and dementia. As yet, there are no specific suggestions for its clinical application. This is predominantly because the etiology of greater eGFR

variability remains uncertain, above and beyond a proposed dynamic surrogate of kidney resilience. Future studies are required to understand the determinants and correlates of greater eGFR variability. For example, it is uncertain if eGFR variability is a marker of reduced vascular compliance, diminished kidney autoregulatory capacity, vascular calcification, or other as yet unidentified factors. Additional important clinical questions remain, such as defining the normal range of eGFR variability and determining whether eGFR variability has similar clinical significance across the age spectrum. Future studies addressing the above questions in the general population and in unique subgroups will be necessary to determine if, ultimately, specific clinical interventions are indicated in persons with higher variability. In the meantime, because eGFR variability is frequently observed in everyday clinical practice, and because eGFR variability appears to consistently associate with adverse clinical outcomes across studies, clinicians should be alerted that those with marked fluctuations represent a high-risk group, whatever their mean eGFR may be, and may benefit from closer surveillance.

ARTICLE INFORMATION

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