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**In Reply** Because our study was a phase 2B trial with the purpose of finding the optimal dosage with which to conduct a phase 3 outcome trial, strong conclusions should not be drawn from the results. Although Dr Feng and colleagues are correct that change in UACR at day 90 was the primary end point, we understand this is not consistent with any valid renal outcome and is a marker of inflammation and cardiovascular risk rather than renal injury.<sup>1</sup> We are fully aware of the variable relationship of high albuminuria and both kidney disease and cardiovascular outcomes from powered trials.

We did not provide data on blood pressure variability because this was not a prespecified primary or secondary end point, although we are aware of the increased cardiovascular risk associated with increased blood pressure variability. We did perform ambulatory blood pressure monitoring in a subgroup of patients, and these data will be analyzed in the future.

Hypotension was reported as an adverse event in less than 1% of patients; all events were of mild intensity, and none resulted in modification of drug therapy or any action with study drug.

We appreciate the comment about dosing of ACE inhibitors and angiotensin receptor blockers contributing to greater effects on UACR; however, the study did not allow for titration of ACE inhibitors or angiotensin receptor blockers unless blood pressure was significantly elevated. In our trial, there was no significant uptitration of ACE inhibitors or angiotensin receptor blockers. Thus, the data are not confounded by increased dosing of other renin-angiotensin system-blocking therapies.

We agree that outcome studies are needed and we have started studies involving 3 outcomes of diabetic kidney disease: kidney failure, cardiovascular outcomes, and heart failure. The first 2 trials are now recruiting patients and the heart failure trial will start within the next few months.

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**Conflict of Interest Disclosures:** The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Bakris reported receiving grants from Takeda and being a consultant to AbbVie, Takeda, Medtronic, Relypsa, Daiichi-Sankyo, Janssen, Novartis, Bayer, Bristol-Myers Squibb, CVRx, Elcelyx, Eli Lilly/Boehringer Ingelheim, GlaxoSmithKline, Tengion, and ZS Pharma. Dr Nowack reported being an employee of Bayer Pharma AG.

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## Managing Chronic Kidney Disease in Older People

**To the Editor** Dr Levey and colleagues<sup>1</sup> and Dr Glassock and colleagues<sup>2</sup> debated whether age calibration should be required to determine chronic kidney disease (CKD) in older people. However, this is not what matters to patients. The rate of loss of renal function, not age calibration of estimated glomerular filtration rate (eGFR), is what really matters.

The key considerations for older patients with CKD are how fast they are losing renal function, what their life expectancy is, and how to prevent or postpone dialysis.

First, several studies demonstrate that older patients lose renal function slower than younger patients, with periods of stable renal function for years, even with advanced CKD.<sup>3</sup> The rate of renal function loss over time is a predictor of mortality, and rapid loss correlates with an increased probability that dialysis will be required. There are few proven strategies to decrease renal disease progression.

Second, life expectancy is critical for managing disease among older patients with CKD. The possibility of death from CKD needs to be considered in relation to a patient's competitive risk of death from a condition not related to renal failure. For the majority of older patients with CKD, slow loss of renal function and accompanying comorbidities make death before needing dialysis the most likely scenario. In a large cohort study of patients with CKD, the risk of death was more likely than the risk of needing dialysis with age, even with lower initial eGFR levels.<sup>4</sup> For patients older than 85 years, the risk of death always exceeded the risk of needing dialysis.

Third, risk assessment tools have been advocated to predict who will require dialysis. These tools have not been designed to consider competitive risk of death and generally consider an eGFR of less than 15 mL/min/1.73 m<sup>2</sup> the point where a patient will require dialysis.<sup>3</sup> This eGFR cut point is inappropriate when considering the evidence that starting dialysis at eGFR levels greater than 10 mL/min/1.73 m<sup>2</sup> is not beneficial and may be harmful.<sup>5</sup>

The most recent Canadian guideline for dialysis initiation considers the body of evidence and suggests "intent to defer" dialysis until an eGFR of less than 6 mL/min/1.73 m<sup>2</sup> is reached.<sup>5</sup> Urine creatinine level is a determinant of survival, and older patients with decreased muscle mass may have falsely high eGFRs. One can argue that this subgroup of older patients with CKD has a higher competitive risk of a non-renal failure-related death, and thus the intent to defer dialysis may still be in the patient's best interest.

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**Conflict of Interest Disclosures:** The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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4. O'Hare AM, Choi AI, Bertenthal D, et al. Age affects outcomes in chronic kidney disease. *J Am Soc Nephrol*. 2007;18(10):2758-2765.
5. Rosansky SJ, Durkin MW. Starting dialysis at eGFR >5 mL/min per 1.73 m<sup>2</sup>: are we barking up the wrong tree? *Kidney Int*. 2014;86(4):673-675.

**In Reply** We respectfully disagree with Dr Rosansky on several key points and favor a more comprehensive approach to the care of older patients with CKD than he has proposed.

First, the current eGFR and the rate of future decline are each important in the care of older patients with CKD. Numerous studies show the current eGFR is related to a broad range of adverse outcomes beyond kidney failure, including cardiovascular disease, metabolic and hormonal complications, medication toxicity, infections, cognitive impairment, and frailty.<sup>1</sup>

These complications cause decreased quality of life, increased risk for hospitalization, and shorter life expectancy. Even though the rate of future eGFR decline is clearly linked to the likelihood of developing kidney failure, it is difficult to predict (even the past rate of decline is imprecise when based on short periods), and it would be inappropriate for clinicians to overlook complications of the current eGFR while monitoring for its subsequent decline. Clinical practice guidelines are available to assist clinicians in the evaluation and treatment of these complications and should be followed.<sup>2</sup> Of note, management is guided by the urine albumin-to-creatinine ratio (ACR) as well as by eGFR.

Second, validated instruments to predict risk of initiating dialysis or transplantation (not eGFR <15 mL/min/1.73 m<sup>2</sup>) are available and should be used. The Kidney Failure Risk Equation, initially developed in Canada,<sup>3</sup> predicts risk within 2 and 5 years for patients with an eGFR less than 60 mL/min/1.73 m<sup>2</sup>, using age, sex, current eGFR, and urine ACR. Sensitivity analyses using competing risk models did not reveal substantive differences in predictions.

The required clinical data should be available for all patients with CKD, and online calculators are available.<sup>4</sup> We suggest that clinical laboratories use the Kidney Failure Risk Equation to report the risk when serum creatinine and urine ACR are measured and that clinicians incorporate risk prediction into treatment algorithms for older people with CKD. This will provide a more rational basis for decision making than using only eGFR and age.

Third, dialysis can be a lifesaving therapy for patients with symptomatic kidney failure, and the intent of care should not be to defer dialysis until eGFR reaches a predetermined threshold. We agree that data from randomized trials do not show a benefit of dialysis initiation before the onset of uremic symptoms.<sup>5</sup> However, in our view, the observational studies cited in the article by Rosansky and Durkin<sup>6</sup> that show harm from initiation of dialysis at higher vs lower eGFRs based on serum creatinine level are irreparably confounded by non-

GFR determinants of serum creatinine that are associated with higher mortality, such as low creatinine generation from decreased muscle mass.

We suggest that clinicians inform older patients with CKD at high risk about the benefits and risks of dialysis and initiate this therapy in those who desire it when uremic symptoms arise.

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**Conflict of Interest Disclosures:** The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Levey reported that he was the chair of the workgroup for the 2012 KDOQI (Kidney Disease Outcomes Quality Initiative) CKD guideline and a member of the workgroup for the 2012 KDIGO CKD guidelines. Dr Inker reported that she was the co-chair of the workgroup for the 2013 KDOQI commentary on the 2012 KDIGO CKD guideline. Dr Levey reported being the principal investigator and Dr Inker reported being the clinical director for the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) research group, which developed the CKD-EPI equations for GFR estimation. Drs Levey, Inker, and Coresh reported applying for a patent for precise estimation of GFR using a panel of filtration markers. Dr Inker also reported receiving funding from the National Institutes of Health, National Kidney Foundation, Pharmalink AB, and Gilead Sciences; and having a consulting agreement with Otsuka.

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**In Reply** Our Viewpoint concerned the inappropriate overdiagnosis of CKD in older adults using non-age-calibrated eGFR thresholds, as recommended by current guidelines,<sup>1</sup> and the potential adverse effect of placing a label of CKD on persons older than 65 years entirely on the basis of the discovery of an eGFR of 45 to 59 mL/min/1.73 m<sup>2</sup> in the absence of proteinuria or other signs of kidney injury.

Such persons uncommonly display signs of a progressive form of kidney disease, other than the usually slow, age-related decline in eGFR (most commonly <1 mL/min/1.73 m<sup>2</sup> per year),<sup>2</sup> and seldom develop a requirement for treatment of end-stage renal disease,<sup>3,4</sup> thus rendering the "diagnosis" of CKD doubtful.

We do not disagree with Dr Rosansky that the rate of decline of eGFR and the prospect of requiring renal therapy for

end-stage renal disease are both important prognostic aspects of CKD at any age.<sup>5</sup> However, we doubt that adding a requirement for an assessment of renal function trajectory would be a practical additional step for confirming a diagnosis of CKD in an older population with moderate, age-related renal function decline in the absence of markers of renal injury, such as proteinuria.

Such persons also demonstrate no appreciable shortening of remaining life expectancy. Thus, Rosansky's concerns would mainly be applicable to those patients with bona fide CKD of a progressive nature.

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1. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Disease: Improving Global Outcomes (KDIGO)*. [http://www.kdigo.org/clinical\\_practice\\_guidelines/pdf/CKD/KDIGO\\_2012\\_CKD\\_GL.pdf](http://www.kdigo.org/clinical_practice_guidelines/pdf/CKD/KDIGO_2012_CKD_GL.pdf). Accessed November 20, 2015.
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