D etermining the right time to initiate long-term kidney replacement therapy is a challenge. Traditional indications for acute kidney failure include acidosis, electrolyte abnormalities, intoxications, fluid overload, and uremia, with a push toward earlier initiation.2,3 However, indications for chronic kidney failure are more subtle, with uremia the dominant indication for dialysis therapy initiation and conservative treatments potentially available to allow for later dialysis therapy initiation, even for individuals with a very low estimated glomerular filtration rate (eGFR).4 Accordingly, defining uremia is critical for identifying the timing of long-term kidney replacement therapy; unfortunately, there are no definitive signs or symptoms that can reliably identify uremia. One review loosely defined uremia as “the illness accompanying kidney failure that cannot be explained by derangements in extracellular volume, inorganic ion concentrations, or lack of known renal synthetic products.”5 This definition is challenging to translate into day-to-day clinical practice because uremia often is marked by fatigue and lethargy, anorexia, sleep disturbances, and pruritus, none of which are specific to kidney failure.5 However, indications for chronic kidney failure are more subtle, with uremia the dominant indication for dialysis therapy initiation and conservative treatments potentially available to allow for later dialysis therapy initiation, even for individuals with a very low estimated glomerular filtration rate (eGFR).4 Accordingly, defining uremia is critical for identifying the timing of long-term kidney replacement therapy; unfortunately, there are no definitive signs or symptoms that can reliably identify uremia. One review loosely defined uremia as “the illness accompanying kidney failure that cannot be explained by derangements in extracellular volume, inorganic ion concentrations, or lack of known renal synthetic products.”5 This definition is challenging to translate into day-to-day clinical practice because uremia often is marked by fatigue and lethargy, anorexia, sleep disturbances, and pruritus, none of which are specific to kidney failure.5 Accordingly, we rely on our clinical experiences, and pruritus, none of which are specific to kidney failure.

WHAT DOES THIS IMPORTANT STUDY SHOW?

Rosansky et al14 evaluated 81,176 incident hemodialysis patients between 1996 and 2006 in the United States. Data entered on the End-Stage Renal Disease (ESRD) Medical Evidence Form (form 2728) were used to limit the study population to the healthiest individuals, specifically those aged 20-65 years without diabetes or other comorbid conditions, except hypertension. They note that, compared with a reference group with eGFR <5 mL/min/1.73 m², there is a graded increase in mortality risk associated with higher eGFRs. This result mirrors findings in the healthier subgroup in a similar study evaluating incident dialysis patients in the United States in 1996-1999.17 The finding of increased mortality at higher initiation eGFR is robust in the subgroup of individuals with serum albumin levels ≥3.5 g/dL at hemodialysis therapy initiation, with the effects attenuated but not abrogated in time-lag analyses. Interestingly, higher hemoglobin level at dialysis therapy initiation was associated independently with lower mortality risk in multivariable models.

The key question that must be asked is whether initiating therapy at a higher eGFR truly is harmful or if these results are secondary to confounding that cannot be accounted for in this observational study. The investigators make a valiant attempt to control for confounding by limiting their study population;
that higher eGFRs in incident dialysis patients historically and Mortality Study) Wave II cohort showed that higher eGFR in patients with decreased muscle mass was associated with worse outcomes. Second, eGFR based on serum creatinine levels is only an estimate of measured GFR, with eGFR that may appear too high to account for measured GFR would be lower and may require initiation of renal replacement therapy if any of the following are present: symptoms of uremia (after excluding other causes), refractory metabolic complications (hyperkalemia, acidosis), volume overload (manifesting as resistant edema or hypertension) or a decline in nutritional status (as measured by serum albumin, lean body mass or Subjective Global Assessment) that is refractory to dietary intervention (Grade D, opinion). Therefore, the paucity of adjusters and limitations inherent to the data source and eGFR itself, this is not sufficient. First, the investigators rely on the ESRD Medical Evidence Form for data about comorbid conditions. A prior evaluation of the Medical Evidence Form in the CHOICE (Choices for Healthy Outcomes in Caring for ESRD) study showed overall sensitivity of only 0.59, with sensitivity of 0.52 or lower for all comorbid conditions except diabetes, hypertension, and HIV (human immunodeficiency virus) infection, whereas a more recent Veterans Administration study showed sensitivity of 0.57 for identifying epoetin use. The poor sensitivity associated with the Medical Evidence Form indicates that many patients included in this analysis likely had more comorbid conditions than were identified and this population therefore may not be as healthy as claimed. Accordingly, variables that are associated with comorbid conditions, such as higher eGFR (as described next), will assume some of this unaccounted for risk and may be deceivingly associated with worse outcomes. Second, eGFR based on serum creatinine level is only an estimate of measured GFR, with eGFR overestimating measured GFR in people with decreased muscle mass. In such patients, despite an eGFR that may appear too high to account for symptoms of uremia, clinicians may appropriately recognize that measured GFR would be lower and therefore initiate dialysis therapy at this higher eGFR. This recognition that measured GFR is lower than eGFR in patients with decreased muscle mass cannot be captured accurately in retrospective analyses of administrative data sets. Supporting this premise, analyses of the DMMS (Dialysis Morbidity and Mortality Study) Wave II cohort showed that higher eGFRs in incident dialysis patients

Box 1. Excerpts of Current Guidelines for the Initiation of Dialysis Therapy

- **National Kidney Foundation, KDOQI 2006**\(^{37}\): When patients reach stage 5 CKD (estimated GFR <15 mL/min/1.73 m\(^2\)), nephrologists should evaluate the benefits, risks, and disadvantages of beginning kidney replacement therapy. Particular clinical considerations and certain characteristic complications of kidney failure may prompt initiation of therapy before stage 5. (Grade B, moderately strong evidence).

- **Canadian Society of Nephrology 2006**\(^{38}\): No evidence currently exists upon which to recommend a GFR at which renal replacement therapy should be initiated in the absence of complications of chronic kidney disease (grade D, opinion). Patients with an estimated GFR <20 mL/min/1.73 m\(^2\) may require initiation of renal replacement therapy if any of the following are present: symptoms of uremia (after excluding other causes), refractory metabolic complications (hyperkalemia, acidosis), volume overload (manifesting as resistant edema or hypertension) or a decline in nutritional status (as measured by serum albumin, lean body mass or Subjective Global Assessment) that is refractory to dietary intervention (Grade D, opinion).

- **Australian and New Zealand Society of Nephrology, CARI 2005**\(^{28}\): Commence dialysis when GFR falls below approximately 10 mL/min/1.73 m\(^2\) if there is evidence of uremia or its complications such as malnutrition. In occasional patients it may be necessary to initiate dialysis at a higher GFR (Level III evidence). If there is no evidence of uremia or its complications including malnutrition, commence dialysis when GFR falls below approximately 6 mL/min/1.73 m\(^2\) (Level III evidence).

- **ERA-EDTA, 2002**\(^{26}\): Dialysis should be instituted whenever the GFR is <15 mL/min and there is one or more of the following: symptoms or signs of uremia, inability to control hydration status or blood pressure, or a progressive deterioration in nutritional status. In any case, dialysis should be started before the GFR has fallen to 6 mL/min/1.73 m\(^2\), even if optimal predialysis care has been provided and there are no symptoms. High-risk patients e.g. diabetics may benefit from an earlier start [Evidence level: C]. To ensure that dialysis is started before the GFR is <6 mL/min, clinics should aim to start at 8-10 mL/min [Evidence level: C].

- **United Kingdom Renal Association, 2009**\(^{31}\): We recommend that the decision to start RRT in patients with CKD stage 5 (eGFR <15 mL/min/1.73 m\(^2\)) should be based on a careful discussion with the patient of the risks and benefits of RRT taking into account the patient’s symptoms and signs of renal failure, nutritional status, co-morbidity, functional status, and the physical, psychological and social consequences of starting dialysis in that individual (GRADE 1D). We suggest that serious consideration should be given to starting renal replacement therapy in patients with an eGFR <6 mL/min/1.73 m\(^2\), even if the patient is asymptomatic (GRADE 2C).

Abbreviations: CARI, Caring for Australasians with Renal Impairment; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ERA-EDTA, European Renal Association-European Dialysis and Transplant Association; KDOQI, Kidney Disease Outcomes Quality Initiative; RRT, renal replacement therapy.
mortality risk was not observed in those who initiated dialysis earlier.21

**HOW DOES THIS STUDY COMPARE WITH PRIOR STUDIES?**

To date, there are few clinical trials that examine early versus late dialysis therapy initiation. The IDEAL (Initiating Dialysis Early and Late) study randomly assigned 828 patients in Australia and New Zealand with kidney failure to early-start (eGFR, 10-14 mL/min/1.73 m²) or late-start (eGFR, 5-7 mL/min/1.73 m²) dialysis therapy.22 Of those randomly assigned to late start, 75% initiated dialysis therapy at an eGFR >7 mL/min/1.73 m², mostly due to symptoms of uremia. There was no difference in the primary outcome of all-cause mortality between the 2 study groups. Brunori et al4 randomly assigned 112 nondiabetic patients 70 years or older with eGFR of 5-7 mL/min/1.73 m² to either immediate dialysis therapy initiation or observation in conjunction with a supplemented very low-protein diet. Although patients receiving the very low-protein diet initiated dialysis therapy a median of 10.7 months later than the immediate-dialysis group, there was no difference in mortality. In sum, these 2 randomized controlled trials indicate that, in closely monitored populations without symptoms of uremia, targeting later dialysis therapy initiation is safe.

There are multiple observational studies that examine the population-wide association of serum creatinine level and eGFR with mortality. These show the dual role of higher serum creatinine level as a marker of health (muscle mass and nutrition) and a marker of disease (kidney function). In general population studies, lower eGFRs (higher serum creatinine levels) are associated with increased mortality, whereas very high eGFRs (very low serum creatinine levels) also are associated with increased mortality.23-25 Conversely, in prevalent dialysis patients, higher serum creatinine level is a powerful predictor of survival.26 Taken in sum, these data suggest considerable heterogeneity in the association of both eGFR and serum creatinine level with the overall clinical state. In the study by Rosansky et al14 evaluating incident dialysis patients, it is likely that higher eGFR at dialysis therapy initiation (lower serum creatinine level) is more indicative of poorer overall health rather than level of kidney function. This relationship between creatinine level and health status would be more in accordance with the relationship seen in the prevalent dialysis population than in the general population. Observational reports with limited or suspect comorbidity data, such as the study by Rosansky et al,14 cannot overcome the substantial confounding between eGFR and outcomes. Accordingly, their causal attribution that “early start of hemodialysis may be harmful” overreaches the available data and the study design.

**WHAT SHOULD CLINICIANS AND RESEARCHERS DO?**

Recent experiences with interpreting hemoglobin levels provide an important parallel to the question of dialysis therapy initiation. Interestingly, in the study by Rosansky et al,14 higher hemoglobin level at dialysis therapy initiation is associated independently with better outcomes in multivariable models. Does this mean that we should interpret this study as instructing us to push for higher hemoglobin levels at the time of dialysis therapy initiation? If we have learned anything during the past decade, it is that observational data, even those assembled to minimize biases, can still be misleading. This is reinforced by the contrast between the study by Rosansky et al,14 in which initiation at a higher eGFR was associated with higher mortality, and the IDEAL trial, in which there was no difference in mortality between patients randomly assigned to earlier versus later initiation of dialysis therapy.

Current clinical guidelines appropriately are not definitive with respect to a specific eGFR cutoff below which dialysis therapy should be initiated. Rather, all professional societies state that clinical impression, with assessment of symptoms and signs consistent with uremia, is paramount to any GFR cutoff point (Box 1). Given the limited ability of statistical models and administrative data to accurately quantify the variables that a physician assesses in patient encounters, the limitations of serum creatinine level as a marker of GFR, and the importance of balancing patient preferences and values with medical benefit, we would assert that the findings of Rosansky et al14 do little to change what should be current medical practice. Careful interpretation of symptoms and signs, eGFR, and other clinical and laboratory data, taking into account the limitations associated with each of these, is essential to making the best decision regarding initiation of dialysis therapy. Reflecting results from clinical trials, we suggest that the timing of dialysis therapy initiation in individuals with advanced kidney disease should remain focused on individualized decision making guided by clinical judgment, symptom burden, and patient preference.

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