

## Have We Reached the Limit of Mortality Benefit With Our Approach to Renal Replacement Therapy in Acute Kidney Injury?

### Related Article, p. 1116

In this issue of *AJKD*, Jamale et al<sup>1</sup> tackle one of the most difficult and important issues regarding renal replacement therapy (RRT) in acute kidney injury (AKI): the timing of the therapy. The question of when to start RRT has troubled nephrologists for well over a half century<sup>2</sup> and is widely viewed as a top research priority in the field of AKI.<sup>3-5</sup> The study by Jamale et al<sup>1</sup> is an important step forward to answering this question due to the high quality of the trial design. In this study, 208 patients with community-acquired AKI were randomly assigned to early- versus usual-start RRT (intermittent hemodialysis). Early-start RRT was initiated at a serum urea nitrogen (SUN) level >70 mg/dL and/or a serum creatinine level >7.0 mg/dL; usual-start RRT was initiated when complications occurred (eg, refractory hyperkalemia, volume overload, acidosis, nausea, and anorexia). Based on the initial mean Sequential Organ Failure Assessment (SOFA) score, patients were ill and had expected mortality of 33%.<sup>6</sup> The key finding of the study was that, unexpectedly, mortality was not significantly different between patients receiving early- and usual-start hemodialysis: it was 20.5% for early-start and 12.2% for usual-start RRT.

In discussing this study, it is important to consider the issues of power and realistic expectations. The study by Jamale et al<sup>1</sup> is now the largest randomized controlled trial (RCT) of early- versus usual-start RRT in AKI, containing more patients than all other published RCTs on this topic combined. Prior to the Jamale et al<sup>1</sup> study, 5 RCTs were published in peer-reviewed journals (Table 1). Based on their small size and unrealistically large treatment effect (observed or estimated), these trials were underpowered to demonstrate a credible difference in mortality, whether positive or negative. Unfortunately, the trial by Jamele et al<sup>1</sup> also is not definitive due to underpowering. Specifically, the Jamale et al<sup>1</sup> study was powered to detect a 50% relative reduction in mortality from 40% to 20%. Fortunately for the patients, but unfortunately for the trial, overall mortality was

~16%, which greatly reduces the power of the study. The low mortality rate is due in part to the causes of AKI and the patient population, which was relatively healthy with minimal comorbid conditions. Working backwards, assuming mortality of 16% in their study of 208 patients, the study was powered to detect an improvement in mortality to ~4%, or a 75% relative improvement in mortality. Thus, as the authors conclude, a larger multicenter trial of early- versus usual-start RRT is still needed.

To conduct an adequately powered trial of early RRT in the future, a realistic assessment of mortality benefit must be ascertained and expectations must be lowered. Lowering expectations is essential for future RRT trials and for moving beyond RRT-related interventions to treat AKI. Although it has been argued that the approach to RRT is not yet optimized,<sup>7</sup> we need to consider that we may be at the limit of the potential benefit of RRT in AKI and thus further adjustments to RRT in AKI may have little impact on overall mortality. Lowering expectations may be difficult. The development of RRT was driven by a passionate belief that controlling uremic symptoms in patients with AKI would save lives by allowing the time needed for kidney function to recover. Although difficult to fathom, demonstrating that dialysis reduced mortality in AKI was difficult even in the 1950s: it was observed then that despite control of uremic symptoms and normalization of electrolyte disturbances, patients still died of other illnesses, such as sepsis.<sup>2,8</sup> This frustrating observation continues today, and the challenge to demonstrate a reduction in mortality with adjustments to RRT also persists.

What is a realistic mortality benefit for early RRT in AKI? The potential benefit of early RRT specifically was assessed in a meta-analysis that demonstrated a significant 28% risk reduction favoring early RRT in cohort trials and a nonsignificant ( $P = 0.08$ ) 36% risk reduction favoring early RRT in RCTs.<sup>5</sup> Because the potential benefit of any intervention will appear less in an intention-to-treat analysis than in an as-treated analysis, a lower estimate of mortality benefit would be required. For example, in the trial by Jamale et al,<sup>1</sup> 27 (13%) patients recovered kidney function before even receiving RRT and 25 patients (12%), including 18 in the usual-start arm, required emergent RRT (eg, for hyperkalemia or fluid overload). Thus, 25% of participants did not receive RRT at all or received RRT irrespective of the early- or usual-start criteria, but necessarily were included in the intention-to-treat analysis.

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**Table 1.** Published and Hypothetical Randomized Controlled Trials of Early-Start RRT in AKI

Trial	N	AKI Setting	RRT Modality	SUN (mg/dL) in Early- vs Usual-Start RRT	Expected Mortality Reduction <sup>a</sup>	Reduced Mortality With Early-Start RRT?	Observed Mortality With Early-Start RRT	Observed Mortality With Usual-Start RRT	Observed Relative Change in Mortality
Published underpowered trials									
Conger <sup>14</sup> (1975)	18	Post-traumatic	Intermittent HD	50 vs 120	NA	Yes	38%	80%	53% ↓
Pursnani et al <sup>15</sup> (1997)	35	Medical, obstetric	HD	NR <sup>b</sup>	NA	Yes	22%	29%	24% ↓
Bouman et al <sup>16</sup> (2002)	71	ICU (cardiosurgical, surgical, medical)	Continuous hemofiltration	48 vs 105	40% absolute (80% relative <sup>c</sup> )	No	31%	25%	24% ↑ (NS)
Durmaz et al <sup>17</sup> (2003)	44	Post-CABG	Intermittent HD	63 vs NR	NA	Yes	4%	30%	87% ↓
Sugahara & Suzuki <sup>18</sup> (2004)	28	Post-CABG	Continuous HD	NR <sup>d</sup>	NA	Yes	14%	86%	84% ↓
Jamale et al <sup>1</sup> (2013)	208	Community-acquired	Intermittent HD	71 vs 101	20% absolute (50% relative)	No	21%	12%	71% ↑ (NS)
Hypothetical definitive trials <sup>e</sup>									
ICU	1,386	ICU	—	50-60 vs 100	15% relative	—	—	50%	—
High-risk non-ICU	2,894	High-risk non-ICU	—	50-60 vs 100	20% relative	—	—	20%	—
Non-ICU	6,423	Non-ICU	—	50-60 vs 100	20% relative	—	—	10%	—

Abbreviations: AKI, acute kidney injury; CABG, coronary artery bypass grafting; HD, hemodialysis; ICU, intensive care unit; NA, not applicable; NR, not reported; NS, not significant; RRT, renal replacement therapy; SUN, serum urea nitrogen.

<sup>a</sup>Used for power calculation.

<sup>b</sup>Early RRT was defined as SUN < 120 mg/dL or serum creatinine < 7.0 mg/dL.

<sup>c</sup>The anticipated mortality of the control group was not stated; however, if expected mortality were 50%, a 40% absolute risk reduction would be to 10% in the intervention group, or an 80% relative reduction in mortality.

<sup>d</sup>Enrollment criteria were based on urine output; however, at the time of RRT initiation, serum creatinine was 2.9 in early- versus 3.0 mg/dL in usual-start RRT.

<sup>e</sup>Three examples of hypothetical randomized controlled trial sizes with conservative relative mortality benefit are listed. (1) ICU: in this example, the power calculation to determine number of patients needed is based on expected mortality of 50% in order to detect a 15% relative reduction to 42.5% with 80% power and 2-sided  $\alpha = 0.05$ . (2) High-risk non-ICU: in this example, the power calculation to determine number of patients needed is based on expected mortality of 20% in order to detect 20% relative reduction to 16%. (3) Non-ICU: in this example, the power calculation to determine number of patients needed is based on expected mortality of 10% in order to detect 20% relative reduction to 8%. These calculations do not account for dropout.

Realistic mortality benefit for RRT in AKI also may be derived from the Veterans Affairs/National Institutes of Health ATN (Acute Renal Failure Trial Network) trial (n = 1,124),<sup>9</sup> which was powered to detect an 18% relative reduction in mortality (from 55% to 45%), and the RENAL (Randomized Evaluation of Normal Versus Augmented Level of Replacement Therapy) trial (n = 1,508),<sup>10</sup> which was powered to detect a 14% relative reduction in mortality (from 60% to 52%) with intensive RRT dosing. Both studies found no mortality benefit with intensive RRT. Because the power was robust, results were convincing and have set the standard of dosing guidelines for RRT.<sup>4</sup> Thus, a 15%-20% relative mortality reduction is a reasonable target for an early-start RRT trial, and demonstrating this level of benefit would certainly change clinical practice.

What is early RRT? The inability to agree on what constitutes early RRT is another fundamental barrier that has prevented a multicenter trial from being conducted. Jamale et al<sup>1</sup> used serum creatinine and SUN levels to define early-start RRT. Although the limitations of serum creatinine and SUN levels are well known, this biochemical definition for a definitive trial of early RRT has many advantages. Specifically, the definition is simple and easily applicable to clinical practice: the vast majority of studies of early- versus usual-start RRT previously have been based on SUN level, clinical experience with SUN and serum creatinine levels to identify AKI is vast, and certain practice guidelines regarding RRT initiation are even based on SUN levels. Although there is great hope that emerging biomarkers may assist in appropriate clinical trial randomization, the current use of biomarkers for clinical trial enrollment in AKI remains controversial. Thus, a definitive study of early- versus usual-start RRT reasonably could look like the present study, with early-start RRT defined as SUN level <70 mg/dL (perhaps 50-60 mg/dL) and usual-start RRT being initiated with an SUN level of 100 mg/dL; as in the present study, the usual indications for RRT (eg, hyperkalemia and volume overload) would remain in place. Given the Acute Dialysis Quality Initiative (ADQI) recommendations suggesting that SUN level should not increase to >100 mg/dL before RRT is initiated, the usual-timing RRT arm reasonably should be capped at 100 mg/dL.<sup>11</sup>

An additional concern regarding early-start RRT is that patients who otherwise might recover their kidney function may be subjected to unnecessary RRT and potentially experience complications. In particular, RRT may delay recovery from AKI, possibly due to the hemodynamic stress of RRT and resultant decreased kidney perfusion. Although a meta-analysis found that there may be a benefit of early RRT,<sup>12</sup> the present study found that kidney

recovery was delayed in the early-start group by 2 days; thus, the effect of early RRT on kidney recovery remains unknown. A recent meta-analysis found that modality of RRT may affect kidney recovery, with intermittent hemodialysis being associated with an increased risk of dialysis dependence versus continuous RRT in a pooled analysis of observational studies; notably, however, this association was not found in pooled analysis of RCTs, which suggests that the effect of modality may have been due to study allocation bias, rather than a true effect on kidney recovery.<sup>13</sup> Although avoiding the potential harm of early RRT is an important concern, withholding a potentially life-saving procedure is even more unsettling. Because it still is unknown whether earlier RRT might have a mortality benefit in patients with AKI, an early-start trial of RRT is warranted, although it must be designed carefully to monitor for potential complications, keeping in mind the theoretical effect that modality may have on kidney recovery. Along these lines, reasonable secondary end points might include a composite of major adverse kidney events, such as time to hospital discharge, dialysis dependence, or incomplete recovery of kidney function (eg, a 25% decrease in estimated glomerular filtration rate at 3 months).

In conclusion, nephrologists have struggled with the issue of when to start RRT in patients with AKI for more than 50 years. The trial by Jamale et al<sup>1</sup> demonstrates that an early- versus usual-start RRT trial is feasible and is an excellent model for future trial design. Performing a definitive adequately powered clinical trial of early RRT is the next necessary step to determine whether we have reached the full mortality benefit of RRT in patients with AKI. RRT is our tool; it is time for us know when to use it.

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