Beliefs about when to initiate dialysis in patients with AKI are passionately held by nephrologists, and are—on the whole—unsupported by reliable evidence. Indeed, it may be the very lack of high-quality evidence that gives rise to such impassioned belief systems. It is commendable that the nephrology community has recognized that addressing this lack of evidence should be a major target of research (1). Unfortunately, this research effort has been hindered by a lack of consensus on exactly what the “timing issue” is.

Two main issues hamper research in this area. The first is the tendency for researchers to cast the clinical question in the context of “early” versus “late” dialysis. This thinking inaccurately parallels efforts to define the appropriate initiation of dialysis in the CKD population. In advanced CKD, there is a sense (though it may be misplaced) of the inevitability of dialysis. In that setting, the question of whether to start early, perhaps with an eGFR >10 but <15 ml/min per 1.73 m², versus later, has intuitive appeal (2). In AKI, however, dialysis may not be inevitable. Indeed, a recent study of post-cardiac surgery patients revealed that of those who achieve AKI Network stage 1, only 12% progressed to a higher stage, and of those only 33% went on to receive dialysis (3). Thus, the decision to not initiate dialysis does not merely put off the therapy for some period of time; it may obviate the therapy entirely. Any study that attempts to address the timing question must therefore vociferously acknowledge that patients who do not receive dialysis “early” may recover, or die, without ever receiving dialysis “late.”

The second major issue is a lack of consensus over what the definition of early is. Studies using RIFLE, AKI Network, or Kidney Disease Improving Global Outcomes AKI severity scores have, in general, favored initiation of RRT in the lower stages (4,5). Studies examining time from intensive care unit (ICU) admission to RRT initiation have been more varied but seem to suggest a benefit to initiating dialysis earlier in the ICU course (6–8). Data from the Program to Improve Care in Acute Renal Disease study suggests that outcomes of RRT are superior when the therapy is initiated at a lower BUN (9), although other cohorts have not found a similar relationship (10). Perhaps revealing the critical nature of the definition of “early,” an analysis of the Beginning and Ending Supportive Therapy for the Kidney study revealed that patients who received RRT earlier relative to ICU admission fared better than those who received RRT later. However, when this same population was stratified along the median creatinine at initiation, those initiated at a higher creatinine had improved outcomes. Stratification by BUN had no effect (11).

In this issue of CJASN, Vaara et al. (12) shed light on the timing question by defining a set of classic indications for RRT in AKI, including hyperkalemia, acidosis, and volume overload. Using data from the FINNAKI study (13), a prospective, multicenter ICU cohort study in which 33.7% of 2901 patients developed AKI, the authors identify four groups of individuals: those who received RRT within 12 hours of developing conventional indications, those who received RRT >12 hours after developing conventional indications, those who received RRT before conventional indications, and a propensity-matched group of individuals who never received RRT. In terms of 90-day mortality, pre-emptive RRT appeared to be the most effective treatment strategy (the mortality rate was 26.9% compared with 48.5% among those who received RRT for conventional indications).

Prior studies have been limited by the absence of a control group. As mentioned earlier, the salient question is not whether dialysis should be initiated early or late but rather early or not early. This requires the identification of a group of individuals who could reasonably receive dialysis, but didn’t: a tall order for any observational cohort. In the absence of an adequate control, we must constantly wonder if the “early” group, by whatever definition, actually needed dialysis at all. Indeed, if we imagine a world in which all hospitalized patients receive dialysis on admission, we would expect outcomes to be much better than the current state of affairs where only the most ill patients receive the therapy.

Vaara et al. use a propensity score–based matching strategy to overcome this limitation, a technique employed by a few other groups, including our own (14,15). While we did not find a benefit to early initiation of dialysis (rather, we found that dialysis was preferable to no dialysis when initiated among those with higher serum creatinine concentrations), we did not use the same definition of “early.”

In the current manuscript, the “classic” indications defined by Vaara et al. are appealing in their breadth, but they may not translate easily into clinical practice.
Indeed, when confronted with a patient with AKI, classic indications may already exist (the median time from ICU admission to RRT indication was 0.5 hours). If we are lucky enough to find a patient with AKI and no classic indications, we would be forced to base our dialysis decision on whether we believe this patient might have similar properties to those that were used to create the propensity-matched cohort. Vaara et al. do not imply, of course, that all ICU patients with AKI should be dialyzed, nor do they identify specific factors (outside of classic indications) that may be reasonable indications. Moving forward, though, we must improve our ability to choose who should receive this therapy.

A randomized trial is an appealing solution to this problem, and several attempts have been made; however, these were underpowered to detect clinically relevant outcomes (16–18). There exist two active trials of dialysis timing in AKI. The Standard versus Accelerated Initiation of RRT in AKI (STARRT-AKI) trial has enrolled 100 critically ill patients with a doubling of serum creatinine and oliguria or an elevated plasma neutrophil gelatinase–associate lipocalin level at 12 centers across Canada (19). Participants were randomly assigned to receive RRT within 12 hours of fulfilling criteria or to usual care. While the primary outcome was protocol adherence, the study will also examine 90-day mortality in both groups. The Initiation of Dialysis Early Versus Delayed in the Intensive Care Unit (IDEAL-ICU) study plans to enroll 864 patients with septic shock meeting RIFLE stage F across 24 ICUs in France (20). Patients will be randomly assigned to receive RRT within 12 hours of meeting eligibility criteria or to RRT 48–60 hours later. Although the investigators have operationalized a definition of “renal recovery” that will allow patients randomly assigned to the delay group to avoid the treatment, the clear preference is that dialysis be performed in most trial participants.

These trials may finally shed light on the bedeviling timing question, but they are really only a beginning. STARRT-AKI, while novel in its use of a biomarker as a potential inclusion criterion, is underpowered to detect significant outcome differences in the two groups, and (by enrolling individuals with only a doubling of creatinine) may have a significant nondialysis rate in the control group. Conversely, the IDEAL-ICU study seems to demand that all patients receive some type of RRT, which may not follow clinical practice in which a “watchful waiting” approach is commonly used (21).

When the decision to start RRT is ambiguous, I am often asked “why not.” Indeed, the overarching trend over time seems to be toward earlier and more continuous dialysis (22). This question speaks to a misunderstood risk-benefit calculus. Like all clinical decisions, the decision of whether to initiate dialysis depends on an appropriate assessment of the risks and benefits of the therapy. But given the paucity of randomized trials of dialysis in AKI, we do not have reliable estimates of risk. Instead, we rely on a general intuition that the benefit of RRT is (for some patients at least) obvious and the risk is minimal. It is possible that we are harming patients with RRT, through either the induction of hypotension or exposure to foreign materials such as catheters and the dialysis membrane itself (23,24). But these risks are often minimized when the discussion of dialysis initiation is breached. It’s clear that this type of thinking will increase resource utilization and costs, especially in the critically ill (25).

There seem to be three approaches available at this point: (1) Perform an extremely large clinical trial, adequately powered to detect outcomes of clinical import, such as mortality, and with enough patients to perform rational subgroup analyses employing various timing criteria; (2) perform multiple smaller clinical trials with extremely carefully defined inclusion criteria; and (3) reconsider our definition of AKI. Although they aren’t ready for broad clinical use, biomarker panels may provide the best window into the physiology of AKI and are increasingly being studied (26–28). Beyond biomarker assays, simply improving prediction rules based on readily available clinical data may allow us to identify a population likely to progress, thus obviating the concern that early RRT will inevitably give treatment to those who might never require it.

Full disclosure: I believe that prompt and prophylactic initiation of RRT is beneficial for certain patients. Unfortunately, I am not sure who those patients are. I remain concerned that the biased evidence favoring early RRT may be putting some patients in harm’s way who would otherwise recover on their own.

Disclosures
None.

References
10. De Corte W, Vanholder R, Dhomt AK, De Waele JJ, Decruyenaere J, Danneels C, Claus S, Hoste EA: Serum urea...
concentration is probably not related to outcome in ICU patients with AKI and renal replacement therapy. *Nephrol Dial Transplant* 26: 3211–3218, 2011


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