Strategies for the optimal timing to start renal replacement therapy in critically ill patients with acute kidney injury

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Renal replacement therapy (RRT) is increasingly utilized to support critically ill patients with severe acute kidney injury (AKI). The question of whether and when to start RRT for a critically ill patient with AKI has long troubled clinicians. When severe complications of AKI develop, the need to commence RRT is unambiguous. In the absence of such complications but in the presence of severe AKI, the optimal time and thresholds for starting RRT are uncertain. The majority of existing data have largely been derived from observational studies. These have been limited due to confounding by indication, considerable heterogeneity in case mix and illness severity, and variably applied definitions for both AKI and for how “timing” was anchored relative to starting RRT. It is unclear whether a preemptive or earlier strategy of RRT initiation aimed largely at avoiding complications related to AKI or a more conservative strategy where RRT is started in response to developing complications leads to better patient-centered outcomes and health services use. This question has been the focus of 2 recently completed randomized trials. In this review, we provide an appraisal of available evidence, discuss existing knowledge gaps, and provide perspective on future research that will better inform the optimal timing of RRT initiation in AKI.


KEYWORDS: acute kidney injury; critical illness; end-stage kidney disease; indications; mortality; multiorgan failure; renal replacement therapy; timing

Acute kidney injury (AKI) is a growing clinical challenge for health care providers.¹–³ AKI, even when mild, has been associated with incremental risk of short- and long-term complications, including chronic kidney disease,⁴ major cardiovascular events,⁵–⁷ sepsis,⁸–¹⁰ gastrointestinal bleeding,¹¹ malignancy,¹² fracture risk,¹³ and death.¹⁴,¹⁵ In a subset of patients perceived to have severe AKI or those in whom clinical and/or metabolic complications related to AKI develop, renal replacement therapy (RRT) is often commenced.¹⁶ Recent trends suggest the growing use of RRT in critically ill patients with AKI.¹⁷–¹⁹ However, the dilemma of whether and when to start RRT for critically ill patients with AKI, in the absence of clearly urgent indications has been unclear and has long been a vexing clinical issue for intensivists and nephrologists.²⁰–²² This issue has been repeatedly identified as a high research priority in the fields of critical care and nephrology.²³–²⁵

In critically ill patients with life-threatening medically refractory complications of AKI (e.g., hyperkalemia, acidemia, fluid overload), there is little controversy about the role for urgent initiation of RRT (Table 1). However, recent observational data have suggested that the occurrence of these “conventional” indications for RRT in critically ill patients with AKI may be less commonly encountered and are generally not the most common primary triggers for starting RRT in routine intensive care unit (ICU) practice.²⁶–²⁸ In these circumstances, RRT is likely started in response to absolute and expected trends in illness severity and nonrenal organ dysfunction, coupled with a subjective perception of benefit by providers (i.e., anticipation of worsening or the low likelihood of kidney recovery).²⁸

The goals of RRT in ICU settings are to achieve and maintain fluid, electrolyte, acid-base, and uremic solute homeostasis along with facilitating additional supportive measures when indicated (i.e., nutritional support, medications, obligatory fluid intake, blood transfusions), while also to prevent overt life-threatening AKI complications from occurring or worsening. Importantly, given the delicate nature of kidney-organ interaction in critically ill states (i.e., kidney-lung, kidney-heart, kidney-brain), RRT might represent an additional important platform of multiorgan support by potentially limiting worsening nonrenal organ dysfunction that may be exacerbated by AKI and overt kidney failure (Table 2). Although these concepts are theoretically
appealing, RRT is associated with potential complications related to both the procedure itself and the need for a dedicated vascular access. As a result, a compelling case may be made for the conservative use of RRT whereby RRT is only started when a life-threatening complication evolves. Ultimately, the controversy surrounding this topic has been stimulated by the absence of high-quality evidence to inform practice. This has contributed to practice variation in the timing of initiation and the use of RRT among critical care units and among individual providers.27,29–32 The lack of strong evidence to guide care has likely contributed to inconsistent and suboptimal quality of care.

In this concise review, we aim to critically appraise current and recently published evidence focused on when to start RRT for ICU patients with AKI, highlight prevailing knowledge and evidence care gaps, provide perspective on existing clinical practice guidelines, and discuss ongoing clinical studies.

**Interaction of RRT and outcome**

RRT, along with mechanical ventilation, vasoactive therapy, and nutritional support, is one of the defining life-sustaining technologies in contemporary critical care. Although a smaller proportion of critically ill patients receive RRT compared with other forms of organ support, its use has progressively expanded.1,17–19 The addition of RRT to the ongoing support of a critically ill patient contributes to an increase in the complexity and costs of care; however, temporal trends in recent decades have shown modest improvements in short-term mortality among those who receive RRT.17

There is fundamental debate about whether RRT may influence patient outcomes or whether, as a supportive therapy in the setting of high illness severity, it is largely a surrogate for the impact of critical illness on outcome. Circumstantial evidence has suggested that receipt of any RRT per se may be independently associated with mortality among ICU patients with AKI.29,33,34 These studies compared outcomes among patients with AKI who received or did not receive RRT. These data likely have methodological limitations commonly encountered in observational studies such as fundamental differences in the populations studied (i.e., case mix, illness severity), residual confounding by indication, and

**Table 1 | Summary of absolute and relative indications and contraindications for starting RRT in critically ill patients with AKI**

<table>
<thead>
<tr>
<th>Absolute indications (in the absence of contraindications to RRT)</th>
<th>Relative indications (in the absence of life-threatening complications of AKI)</th>
<th>Relative contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory hyperkalemia (e.g., K⁺ &gt; 6.5 mmol/l, rapidly increasing, or cardiac toxicity)</td>
<td>Limited physiologic reserve to tolerate the consequences of AKI</td>
<td>Futile prognosis</td>
</tr>
<tr>
<td>Refractory acidemia and metabolic acidosis (e.g., pH ≤ 7.2 despite normal or low arterial pCO₂)</td>
<td>Advanced nonrenal organ dysfunction worsened or exacerbated by excessive fluid accumulation (i.e., impaired respiratory function)</td>
<td>Patient receiving palliative care</td>
</tr>
<tr>
<td>Refractory pulmonary edema due to fluid overload (i.e., diuretic resistant)</td>
<td>Anticipated solute burden (i.e., tumor lysis syndrome, rhabdomyolysis, intravascular hemolysis)</td>
<td>High likelihood of nonrecovery of renal function in patient who is not a candidate for long-term dialysis</td>
</tr>
<tr>
<td>Symptoms or complications attributable to uremia (e.g., bleeding, pericarditis, encephalopathy)</td>
<td>Need for large volume fluid administration (i.e., nutritional support, medications, or blood products)</td>
<td></td>
</tr>
<tr>
<td>Overdose/toxicity from a dialyzable drug/toxin</td>
<td>Severity of the underlying disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Concomitant accumulation of poisons or toxic drugs that can be removed by RRT (i.e., salicylates, ethylene glycol, methanol, metformin)</td>
<td></td>
</tr>
</tbody>
</table>

AKI, acute kidney injury; CKD, chronic kidney disease; RRT, renal replacement therapy.

**Table 2 | Benefits and drawbacks of earlier RRT in the absence of conventional indications among critically ill patients with AKI**

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Drawbacks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoidance and/or early control of fluid accumulation and overload</td>
<td>Need for and complications associated with dialysis catheter insertion (i.e., bleeding, pneumothorax, bloodstream infection)</td>
</tr>
<tr>
<td>Avoidance and/or earlier control of acid-base derangement</td>
<td>Need for and complications associated with anticoagulation regimens</td>
</tr>
<tr>
<td>Avoidance and/or earlier control of electrolyte/metabolic derangement</td>
<td>Risk of iatrogenic episodes of hemodynamic instability that may exacerbate AKI and impede kidney repair/recovery</td>
</tr>
<tr>
<td>Avoidance and/or earlier control of complications of uremia</td>
<td>Risk of excess loss of unmeasured micronutrients and trace elements</td>
</tr>
<tr>
<td>Avoidance of unnecessary or excessive diuretic exposure</td>
<td>Risk of excess clearance or subtherapeutic levels of vital medications (i.e., antimicrobials, antiepileptics)</td>
</tr>
<tr>
<td>Immunomodulation and clearance of inflammatory mediators</td>
<td>Unnecessary exposure to RRT in patients who have a high likelihood of kidney recovery with conservative management</td>
</tr>
<tr>
<td>“Unloading” or “resting” stressed and/or damaged kidneys</td>
<td>Increased bedside workload for providers, resource use, and direct health costs</td>
</tr>
</tbody>
</table>

AKI, acute kidney injury; RRT, renal replacement therapy.
uncontrolled bias (i.e., provider practice variation, information bias).35 Patient-, provider-, and institutional-level factors may all interact to confound the observed association between RRT and outcome, including the decision to offer (or not) RRT and/or to start RRT. However, just as likely is that these studies have included a significant proportion of patients in whom RRT was not likely to modify outcome (Figure 1). As an example, a high degree of use of RRT in patients with a very low survival probability (i.e., advanced chronic illness or severe acute illness) can represent an important source of bias as these patients will likely shift the association to suggest that RRT itself increases the risk of a poor outcome.56 Alternatively, the inclusion of patients with less severe AKI who are started on RRT in settings of marginal (relative) indications where there is a high likelihood of kidney recovery can also confound the association of RRT and outcome as these patients may be likely to survive regardless of whether RRT was received.57 In this circumstance, it is conceivable that the risk and/or harm associated with RRT per se could potentially outweigh the benefit among those with a marginal indication. Interestingly, additional data derived from observational studies in critically ill patients in whom conventional indications for RRT develop have suggested that starting RRT may improve survival.15,38

Defining “timing” relative to starting RRT

There has been little consensus on how best to define “timing” relative to starting RRT in AKI. Retrospective observational studies have used a wide spectrum of arbitrary definitions for “early” and “delayed” or “late” initiation of RRT.39–41 Definitions across studies have integrated physiologic parameters (e.g., urine output), biochemical parameters (e.g., serum creatinine, urea), time relative to the development of AKI (also variably defined), time relative to hospital or ICU admission, and time relative to the development of a recognized clinical or biochemical complication of AKI or a “conventional” indication for RRT such as hyperkalemia, metabolic acidosis, fluid overload, and uremia.39,41,42 It is important to acknowledge that the terms “early” and “late” are relative and what may represent “early” RRT in one circumstance (i.e., clinical context for a given patient or operational definition in a study) may be “late” in another circumstance where the constellation of clinical characteristics, diagnoses, and illness severity differ. The heterogeneity in operational definitions for “timing” or “thresholds” or “criteria” in particular from observational data (often with variable designs and methodological quality) has likely impeded clear inferences to guide clinical practice regarding this issue.

Indeed, Conger43 was first to recognize the challenge in interpreting the emerging literature at the time due to the “the variability of the meaning of the term “early” or “prophylactic” as used by different centers to describe their criteria” for starting RRT. Early nonrandomized studies that examined the timing of initiation of RRT in patients with AKI predominantly used classic biochemical parameters, metabolic acidosis, fluid overload, and uremia.39,41,42 It is important to acknowledge that the terms “early” and “late” are relative and what may represent “early” RRT in one circumstance (i.e., clinical context for a given patient or operational definition in a study) may be “late” in another circumstance where the constellation of clinical characteristics, diagnoses, and illness severity differ. The heterogeneity in operational definitions for “timing” or “thresholds” or “criteria” in particular from observational data (often with variable designs and methodological quality) has likely impeded clear inferences to guide clinical practice regarding this issue.

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such as serum urea concentration and overt uremic symptoms, to discriminate the early or prophylactic start of RRT.20,42–45

In an attempt to further evaluate the timing of RRT initiation in relation to the broader clinical context, Vaara et al.38 evaluated 239 critically ill patients treated with RRT across 17 ICUs in Finland. Individuals who commenced RRT without the presence of a conventional indication were considered to have started “preemptively.” They were compared with patients who started RRT with at least 1 “classic” indication including hyperkalemia, severe acidemia, uremia, oligoanuria, and fluid overload with pulmonary edema. The “classic” group was further classified as “urgent” if started within 12 hours of the development of one of these indications and “delayed” if >12 hours elapsed after the development of one of these indications. In multivariable and propensity-adjusted analyses, classic initiation of RRT was associated with higher 90-day mortality rate compared with RRT that was started preemptively (adjusted odds ratio: 2.1; 95% confidence interval 1.0–4.1). In addition, the 90-day mortality rate was also higher among patients treated with “classic – delayed” RRT compared with those in whom RRT was commenced within 12 hours of an indication appearing (adjusted odds ratio 3.9; 95% confidence interval 1.5–10.2).

A unifying feature of observational studies in this field has been the general focus on patients who received RRT without considering individuals with equally severe AKI who did not receive RRT.29,33,34 Although clinicians may have difficulty prospectively identifying such patients, it is well-known that a significant minority of patients will survive and recover kidney function despite severe AKI without ever receiving RRT. The exclusion of such patients from observational studies has likely led to the “late” groups becoming disproportionately augmented by individuals with poor prognoses. This fact may have led to the gross overestimation of a favorable association between early RRT initiation and survival in observational studies.39–41

Rationale for earlier start of RRT
There is physiologic rationale for why earlier initiation of RRT in critically ill patients with severe AKI, even in the absence of conventional indications, may confer benefit, in particular in circumstances in which there is a perception that recovery from AKI is not imminent.46 Earlier RRT can theoretically facilitate more rapid correction of electrolyte and acid–base derangements and control of uremia and mitigate fluid accumulation (Table 2). Earlier RRT would certainly prevent the occurrence of overt complications of AKI.13 The role of RRT to modulate inflammation/immune function in septic and other vasoplegic states is hypothetically attractive but remains controversial.47,48 The practice of earlier initiation of RRT in critically ill patients with AKI would appear to confer numerous benefits and is currently supported predominantly by observational data and small clinical trials.39,41,42,49–51

Rationale for a conservative approach to starting RRT
There are also potential downsides regarding an earlier start of RRT in the absence of conventional indications (Table 2). These patients will require insertion of a central venous dialysis catheter, will have their blood exposed to an extracorporeal circuit, and will likely receive some form of continuous anticoagulation to maintain circuit patency (i.e., systemic heparin, regional citrate). The potential for exposure to episodes of hemodynamic instability due to excessive ultrafiltration or rapid changes in osmolality may contribute to iatrogenic delays in kidney recovery.52 This is particularly relevant for patients who may have been started on RRT for relatively marginal indications.37 In addition, starting a critically ill patient on RRT adds to bedside workload and resource utilization. A number of randomized trials have not shown incremental benefit for improved outcomes with earlier initiation of RRT in the absence of conventional indications.53–56 These data would imply that the perceived benefit for the earlier initiation of RRT would have to naturally be balanced with the resource implications and potential for harm within the context of the patient’s and family’s preferences for care.57

Current clinical practice guideline recommendations
A number of organizations have published practice guidelines that include statements on timing of the initiation of RRT in critical care settings (Table 3). In 2012, the Kidney Disease Improving Global Outcomes (KDIGO) consortium made 2 statements regarding the timing of RRT initiation in AKI, neither of which was graded. The first was a straightforward recommendation to initiate RRT “emergently when life-threatening changes in fluid, electrolyte, and acid–base balance exist”.24 The second statement asked physicians to consider the “broader clinical context, the presence of conditions that can be modified with RRT, and trends of laboratory tests—rather than single BUN and creatinine thresholds alone—when making the decision to start RRT”.24 Although the latter recommendation might be viewed as overly vague by granting clinicians the “license” to deploy subjective parameters in their decision making, it is nonetheless a reasonable reflection of sound bedside practice in which clinicians evaluate an individual patient’s overall condition rather than a single physiologic or biochemical parameter and weigh the relative risks and benefits for deciding on when to start RRT. In 2013, the National Institute for Health and Care Excellence (NICE) in the United Kingdom published official recommendations that are similar to KDIGO.25 The NICE guidelines also acknowledged the evidence void to guide decision making on this issue. The guidelines further emphasized that clinicians need better tools, such as clinical risk prediction scores and novel point-of-care tests (i.e., novel kidney damage biomarkers) that can incrementally discriminate patients who have a high likelihood of the development of worsening AKI and may benefit from the earlier start of RRT from those who have a high likelihood of rapid recovery of kidney function and who may
Table 3 | Summary of clinical practice guidelines for starting RRT in critically ill patients with AKI

<table>
<thead>
<tr>
<th>Organization</th>
<th>Recommendations</th>
</tr>
</thead>
</table>
| Kidney Disease: Improving Global Outcomes (KDIGO) | (i) Initiate RRT emergently when life-threatening changes in fluid, electrolyte, and acid-base balance exist (not rated).  
(ii) Consider the broader clinical context, the presence of conditions that can be modified with RRT, and trends of laboratory tests rather than single BUN and creatinine thresholds alone when making the decision to start RRT (not rated). |
| National Institute for Health and Care Excellence (NICE) | (i) Discuss any potential indications for RRT with a nephrologist, pediatric nephrologist, and/or critical care specialist immediately to ensure that the therapy is started as soon as needed.  
(ii) Refer adults, children, and young people immediately for RRT if any of the following are not responding to medical management:  
  - Hyperkalemia  
  - Metabolic acidosis  
  - Complications of uremia (i.e., pericarditis, encephalopathy)  
  - Fluid overload  
  - Pulmonary edema  
(iii) Base the decision to start RRT on the condition of the adult, child, or young person as a whole and not on an isolated urea, creatinine, or potassium value. |
| French Intensive Care Society (SRLF) | (i) RRT should be initiated without delay in life-threatening situations (hyperkalemia, metabolic acidosis, tumor lysis syndrome, refractory pulmonary edema). (Expert opinion; strong agreement)  
(ii) The available data are insufficient to define optimal timing of initiation of RRT outside life-threatening situations. (Expect opinion; strong agreement)  
(iii) In children, fluid and sodium overload probably >10%, and very probably >20% should be considered as one of the criteria for initiation of RRT. (Expert opinion; poor agreement)  
(iv) “Early” initiation of RRT means at KDIGO stage 2 or within 24 hours after onset of acute renal failure of which reversibility seems unlikely. (Expert opinion; poor agreement)  
(v) “Late” initiation of RRT means >48 hours after onset of acute renal failure, KDIGO stage 3, or when a life-threatening situation arises because of acute renal failure. (Expert opinion; poor agreement) |

AKI, acute kidney failure; BUN, blood urea nitrogen; RRT, renal replacement therapy.

best be supported by a conservative strategy. In 2015, the French Intensive Care Society (SRLF) also published official recommendations for the application of RRT in ICU settings, including several statements regarding when to start RRT. Each of these organizations acknowledged the limitations of current evidence and associated clinical uncertainty, with each recommending that additional high-quality randomized trials be performed to better inform best practice.24,25,57

Clinical trials focused on the timing of RRT initiation in AKI

A number of randomized trials have attempted to establish the optimal circumstances for starting RRT in AKI (Tables 4 and 5). Three small trials published more than a decade ago focused on patients in whom AKI developed after cardiac surgery with cardiopulmonary bypass.49,50,53 In the largest of these trials, Bouman et al.55 randomized 106 critically ill patients with oliguric AKI who required mechanical ventilation to early (within 12 hours of meeting entry criteria and spread across 2 groups who were also randomized to higher or lower hemofiltration rates) or late (following development of either urea >40 mmol/l, serum potassium >6.5 mmol/l, or severe pulmonary edema; all patients received lower volume hemofiltration) RRT initiation. There was no significant difference in 28-day mortality between the early and late RRT initiation groups; however, given the small sample size, this trial was underpowered for the detection of more modest and realistic treatment effects and lacked generalizability beyond the setting of cardiac surgery–associated AKI.

More recently, Jamale et al.55 reported a larger trial of 208 hospitalized patients with community-acquired AKI randomized to early RRT, defined as starting RRT for a serum urea >23 mmol/l or serum creatinine >618 μmol/l, or standard of care, for which RRT was initiated in the presence of refractory hyperkalemia, acidosis, or volume overload or in the setting of uremic symptoms. No differences in mortality or recovery of kidney function were found. However, the wider applicability of these findings is limited due to the young age of enrolled patients (mean age, 42 years), the spectrum of illnesses contributing to AKI (>50% tropical infections or obstetric complications), and because not all patients were critically ill.

Recently, the STandard vs Accelerated initiation of Renal Replacement Therapy in Acute Kidney Injury (STARRT-AKI) trial was completed56 (Table 4). This was a Canadian multicenter pilot randomized clinical trial that proved the feasibility and safety of performing a larger pragmatic trial comparing early/accelerated RRT with a conservative strategy for starting RRT based on persistent AKI and/or the development of more conventional indications. Importantly, this pilot trial was not designed or powered to inform on important patient-centered outcomes. In total, 101 patients were randomized. The median time from eligibility to starting RRT in the accelerated group was 7.4 hours, whereas in the standard arm, 63% of patients started RRT after a median 31.6 hours. The remaining 25% of patients experienced kidney recovery and did not have RRT started, whereas 12% died
<table>
<thead>
<tr>
<th>Study</th>
<th>Time period</th>
<th>Size</th>
<th>RRT modality</th>
<th>Patient population</th>
<th>Intervention</th>
<th>Control</th>
<th>Outcome (early RRT vs. control)</th>
<th>Additional comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conger</td>
<td>Vietnam War (pre-1975)</td>
<td>N = 18</td>
<td>IHD</td>
<td>Adult, major trauma</td>
<td>Urea &gt; 17.8 mmol/l or SCr &gt; 442 μmol/l</td>
<td>Urea &gt; 42.8 mmol/l or SCr &gt; 884 μmol/l</td>
<td>Mortality: 38% versus 80%</td>
<td>-</td>
</tr>
<tr>
<td>Pursnani et al.</td>
<td>N/A</td>
<td>N = 35</td>
<td>IHD</td>
<td>Adult medical/obstetric</td>
<td>Urea &gt; 42.8 mmol/l or SCr &gt; 619 μmol/l</td>
<td>Clinical decision</td>
<td>Mortality: 22% versus 29%</td>
<td>↓ Complications and hospital stay in early RRT</td>
</tr>
<tr>
<td>Sugahara and Suzuki</td>
<td>1995–1997</td>
<td>N = 28</td>
<td>PIRRT</td>
<td>Adult cardiac surgery</td>
<td>UO &lt; 30 ml/h × 3 h and SCr &lt; 44 μmol/l per d</td>
<td>UO &lt; 20 ml/h × 2 h and SCr &gt; 44 μmol/l per day</td>
<td>Mortality (14 d): 14% versus 86% (P &lt; 0.01)</td>
<td>2 patients in “early” group were still on RRT at day 14</td>
</tr>
<tr>
<td>Durmaz et al.</td>
<td>1999–2001</td>
<td>N = 44</td>
<td>IHD</td>
<td>Adult CKD, cardiac surgery</td>
<td>10% ↑ SCr from preoperative value</td>
<td>≥ 50% increase in SCr or UO &lt; 400 ml/24 h</td>
<td>Mortality: 5% versus 30% (P = 0.048)</td>
<td>↓ Complications and ICU stay in early RRT</td>
</tr>
<tr>
<td>Bouman et al.</td>
<td>1998–2000</td>
<td>N = 106, 2 centers</td>
<td>CVVH</td>
<td>Adult, critically ill, shock</td>
<td>UO &lt; 30 ml/h × 6 h and CrCl &lt; 20 ml/min</td>
<td>Urea &gt; 40 ml/l or K⁺ &gt; 6.5 mmol/l or pulmonary edema</td>
<td>Mortality (28 d): 29% versus 25% (P = 0.8)</td>
<td>4 patients in control recovered before RRT was started</td>
</tr>
<tr>
<td>Jamale et al.</td>
<td>2011–2012</td>
<td>N = 208</td>
<td>IHD</td>
<td>Adult community-acquired AKI</td>
<td>Urea &gt; 25 mmol/l and/or SCr &gt; 619 μmol/l</td>
<td>Conventional indication for RRT (per consensus decision by 2 nephrologists)</td>
<td>Mortality (hospital): 21% versus 12% (P = 0.2)</td>
<td>13% recovered kidney function and 12% received emergency RRT in control</td>
</tr>
<tr>
<td>STARRT-AKI pilot</td>
<td>2012–2014</td>
<td>N = 100</td>
<td>MC</td>
<td>Adult critically ill</td>
<td>Two of: SCr &gt; 2 × baseline; UO &lt; 6 ml/kg × 12 h; blood NGAL &gt; 400 ng/ml</td>
<td>Conventional indicator for RRT</td>
<td>Mortality (90 d): 38% versus 37% (P = 0.6)</td>
<td>Trial design proven feasible</td>
</tr>
</tbody>
</table>

AKI, acute kidney injury; CKD, chronic kidney disease; CrCl, creatinine clearance; CVVH, continuous venovenous hemofiltration; DD, dialysis dependence; ICU, intensive care unit; IHD, intermittent hemodialysis; MC, multicenter; N/A, not available; NGAL, neutrophil gelatinase-associated lipocalin; PIRRT, prolonged intermittent renal replacement therapy; RRT, renal replacement therapy; SC, single center; SCr, serum creatinine; UO, urine output.
before the initiation of RRT. There was no evidence of any tendency to harm in either study arm. This pilot phase informed the design of the principal trial, including simplification of eligibility criteria and the omission of point-of-care testing for whole-blood neutrophil gelatinase-associated lipocalin for the determination of severe AKI, which, in this context, was not found to incrementally identify those most at risk.

**Recent trials examining RRT initiation strategies in AKI.** Early 2016 was marked by the publication of 2 high-profile trials that were designed to evaluate the impact of 2 very different RRT initiation strategies on mortality in critically ill patients with severe AKI. The Early Versus Late Initiation of Renal Replacement Therapy In Critically Ill Patients With Acute Kidney Injury (ELAIN) trial was a single-center randomized trial of 231 critically ill patients that tested whether early RRT, defined as starting RRT within 8 hours of fulfilling KDIGO stage 2 AKI, would improve patient survival compared with delayed RRT, defined as starting RRT within 12 hours of the development of KDIGO stage 3 AKI or upon an absolute indication ensuing (e.g., hyperkalemia, oligoanuria, hypermagnesemia, organ edema resistant to diuretics)\(^\text{21}\) (Table 5). Eligible patients were required to have plasma neutrophil gelatinase-associated lipocalin \(>150\) mg/ml and at least 1 of the following criteria: sepsis, fluid overload, worsening sequential organ failure assessment score, or receipt of vasoactive support. In total, 231 patients, virtually all of whom had AKI in the postoperative setting, were randomized. All patients in the early group received RRT, as did 91% of patients in the delayed RRT group, with the primary indication to commence RRT being the achievement of KDIGO stage 3 AKI. The median difference in RRT initiation from randomization between the 2 interventions was following 21 hours (interquartile range, 18–24). The early RRT intervention conferred a 15.4% absolute reduction in 90-day mortality (39.3% vs. 54.7%; \(P = 0.03\) compared with delayed RRT). Early RRT also led to a higher likelihood of dialysis independence and shorter duration of RRT (9 vs. 25 days, \(P = 0.04\)), and shortening of hospital stay (51 vs. 82 days, \(P < 0.001\)). Early RRT also showed a reduction in 2 proinflammatory mediators (interleukin-6 and -8), whereas there were no differences in additional selected mediators assessed. Of note, use of plasma neutrophil gelatinase-associated lipocalin \(>150\) mg/ml for eligibility did not appear effective for excluding patients at low risk in this trial (only 6 patients).

The Artificial Kidney Initiation in Kidney Injury (AKIKI) trial was a multicenter randomized trial that tested whether a delayed strategy of RRT initiation would confer improved survival among 620 critically ill patients with severe AKI who were receiving mechanical ventilation and/or vasoactive support\(^\text{23}\) (Table 5). The early strategy entailed starting RRT within 6 hours of fulfilling KDIGO stage 3 AKI, and the delayed strategy called for starting RRT only with the development of conventional indications associated with worsening AKI (e.g., oliguria or anuria for \(>72\) hours after randomization, uremia, hyperkalemia, metabolic acidosis, and/or pulmonary edema due to fluid overload). The delayed

<table>
<thead>
<tr>
<th>Feature</th>
<th>ELAIN(^\text{21})</th>
<th>AKIKI(^\text{23})</th>
<th>IDEAL-ICU(^\text{26})</th>
<th>STARRT-AKI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country</td>
<td>Germany</td>
<td>France</td>
<td>France</td>
<td>Canada</td>
</tr>
<tr>
<td>No. of sites</td>
<td>1</td>
<td>31</td>
<td>24</td>
<td>&gt;60</td>
</tr>
<tr>
<td>Setting/population</td>
<td>Mixed medical/surgical ICU (94.8% surgical)</td>
<td>Mixed medical/surgical ICU (79.7% medical)</td>
<td>Mixed medical/surgical ICU (septic shock)</td>
<td>Mixed medical/surgical ICU</td>
</tr>
<tr>
<td>ARR for sample size calculation</td>
<td>18%</td>
<td>15%</td>
<td>10%</td>
<td>6%</td>
</tr>
<tr>
<td>Control group mortality</td>
<td>55%</td>
<td>55%</td>
<td>55%</td>
<td>40%</td>
</tr>
<tr>
<td>Interventions</td>
<td>Early</td>
<td>KDIGO stage 2 (within 8 h)</td>
<td>KDIGO stage 3 (within 6 h)</td>
<td>KDIGO stage 3(^b) (within 12 h)</td>
</tr>
<tr>
<td>Time difference</td>
<td>25.5 h</td>
<td>57.0 h</td>
<td>N/A</td>
<td>41.6 h(^c)</td>
</tr>
<tr>
<td>Received RRT in delayed</td>
<td>90.8%</td>
<td>51.0%</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>RRT modality</td>
<td>Continuous RRT</td>
<td>Physician discretion (initial IHD 55%)</td>
<td>Physician discretion</td>
<td>Physician discretion</td>
</tr>
<tr>
<td>SOFA score of enrolled patient</td>
<td>~16.0</td>
<td>~10.9</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>90-d mortality</td>
<td>60-d mortality</td>
<td>90-d mortality</td>
<td>90-d mortality</td>
</tr>
<tr>
<td>Early</td>
<td>39.3%</td>
<td>48.5%</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Delayed</td>
<td>54.7%</td>
<td>49.7%</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

ARR, absolute risk reduction; ICU, intensive care unit; IHD, intermittent hemodialysis; KDIGO, Kidney Disease Improving Global Outcomes; N/A, not available; RIFLE, risk, injury, failure, loss, end-stage; RRT, renal replacement therapy; SOFA, sequential organ failure assessment.

\(^\text{21}\)Planned enrollment.

\(^\text{26}\)IDEAL-ICU protocol utilizes the RIFLE classification for AKI. RIFLE-F generally aligns with KDIGO stage 3.

\(^b\)Based on STARRT-AKI pilot data.
strategy was not associated with an improvement in 60-day mortality (49.7% vs. 48.5% in the early group, \( P = 0.79 \)). The use of RRT was significantly different between the strategies, with only 51% of patients in the delayed RRT strategy receiving RRT compared with 98% in the early RRT strategy. The median difference for starting RRT between strategies was 57 hours (interquartile range, 25–83) among those actually receiving RRT. In the delayed strategy, the number of RRT-free days was greater (19 vs. 17 days, \( P < 0.001 \)), and the occurrence of catheter-related bloodstream infections was lower (5% vs. 10%, \( P = 0.03 \)), compared with the early strategy. There was no difference in key secondary outcomes including ventilator and vasoactive-free days through day 28, ICU length of stay, hospital length of stay, and dialysis dependence at day 60.

The ELAIN and AKIKI trials are important achievements for critical care nephrology and effectively disproved the notion that well-designed trials comparing RRT initiation strategies in the ICU were too daunting to successfully execute. However, in addition to the confusion created by their discrepant results, there are several issues that clinicians should consider when determining how to integrate the results of these trials into clinical practice. First, despite being the largest to date, both were reasonably small trials that were underpowered to detect plausible differences in mortality that might be mediated by different RRT initiation strategies. For example, AKIKI was designed to detect a 15% absolute reduction in mortality for the delayed compared with the early strategy. Although conceivable that a delayed strategy may translate into fewer RRT-related complications, such an expected survival difference has rarely, if ever, been seen in trials in critically ill patients.60–62 The ELAIN trial calculated a sample size based on an estimated 55% mortality at 90 days (actual observed, 55%), assuming an expected 18% absolute reduction in mortality, an estimate derived largely from observational data. Although it demonstrated a mortality reduction with early RRT, the ELAIN trial had a low Fragility Index of 3 (i.e., 3 more deaths in the early group or 3 fewer deaths in the delayed group would result in a nonsignificant result), implying that the findings of this trial may be imprecise. As a comparison, the sample size calculation for the Randomized Evaluation of Normal versus Augmented Level Replacement Therapy (RENAI) trial used an 8.5% absolute 90-day mortality reduction, assuming a baseline rate of 60% (\( N = 1500 \)) (actual observed, 45%), whereas the Veterans Affairs/National Institutes of Health Acute Renal Failure Trail Network (ATN) trial used a 10% absolute reduction in 60-day mortality assuming a baseline rate of 55% (\( N = 1164 \)) (actual observed, 52%).

Second, the threshold criteria for commencing RRT in the early RRT arms of both trials and the delayed RRT group in ELAIN trial were based on fulfilling KDIGO staging for AKI (i.e., changes to serum creatinine and urine output). While this approach as has been recommended in guidelines,63 the trials effectively used different “timing” thresholds based on the KDIGO criteria. The ELAIN trial used KDIGO stage 2 for early RRT and KDIGO stage 3 for delayed RRT, whereas the AKIKI trial used KDIGO stage 3 for early RRT and conventional indications for delayed RRT. The use of relatively fixed thresholds for triggering RRT in these studies may have contributed to an element of practice misalignment for starting RRT in both groups of the ELAIN trial and the early strategy of AKIKI trial64 (Figure 1). Some aspect of this may be unavoidable when designing an unblinded trial evaluating the timing of the initiation of RRT; however, it also has the potential to question the applicability to decision making at the bedside when clinicians are likely to integrate the broader clinical picture when making the decision to start RRT. In the end, these observations would suggest that a proportion of patients who entered the AKIKI and ELAIN trials were not individuals for whom RRT would be considered in usual practice. Indeed, in 4 recent randomized trials, 10% to 49% of patients with severe AKI allocated to receive delayed RRT survived and recovered kidney function without having received RRT.51,53,54,56 In considering these complexities, commentaries on these 2 trials have stated that further clinical trials are needed.64–66

A pooled analysis including recently completed randomized trials comparing the impact on mortality of early and delayed initiation of RRT in critically ill patients with AKI is shown in Figure 2.

![Figure 2](image-url)
Future randomized clinical trials examining RRT initiation strategies in AKI

Two ongoing randomized trials will perhaps bring further clarity to the question of optimal conditions for RRT initiation in the ICU. The Initiation of Dialysis EARly versus Late in the Intensive Care Unit (IDEAL-ICU), a 24-site study in France will enroll 864 critically ill patients with septic shock and AKI (ClinicalTrials.gov Identifier: NCT01682590). Patients who meet criteria for KDIGO stage 3 AKI within the first 48 hours of septic shock are eligible. “Early” RRT is defined as starting RRT within 12 hours of eligibility, whereas “delayed” RRT is defined as RRT being deferred for at least 48 hours (but no more than 60 hours) from the onset of stage 3 AKI, unless confronted with conventional “absolute” indications (Table 5). The primary endpoint is 90-day mortality.

The main phase of STandard vs Accelerated initiation of Renal Replacement Therapy in Acute Kidney Injury (STARRT-AKI) trial (ClinicalTrials.gov Identifier: NCT02568722), which aims to enroll 2866 critically ill patients with KDIGO stage 2 AKI who do not have a conventional indication for starting RRT. The most responsible clinicians (i.e., intensive care physician and nephrologist) will be asked to affirm clinical equipoise regarding enrollment for each eligible patient. In circumstances in which the most responsible clinicians perceive that immediate RRT is mandated or that kidney recovery is imminent and RRT should be deferred, the patient is excluded. The early/accelerated strategy is defined by starting RRT within 12 hours of fulfilling eligibility, whereas the standard strategy constitutes a protocolized period of “watchful waiting” in which RRT will be discouraged unless at least 1 of the following conventional indications arise(s): serum potassium $\geq 6.0$ mmol/l, pH $\leq 7.20$ or serum bicarbonate $\leq 12$ mmol/l, evidence of severe hypoxemia ($P_{aO_2}/F_{iO_2} \leq 200$) attributable to fluid overload, or persistence of AKI for 72 hours. The primary
endpoints is 90-day mortality. A recently published 100-patient multicenter pilot trial highlighted the feasibility of executing the STARRT-AKI protocol. The successful completion of these 2 trials will provide a 3-fold increase in the total number of critically ill patients with AKI enrolled in randomized trials evaluating strategies, early versus delayed, for starting RRT. These data will certainly work to reconcile the widely discordant findings from the 2 largest trials published to date, AKIKI and ELAIN. The STARRT-AKI trial has a relatively pragmatic design, which will improve confidence in the generalizability and inferences for guiding clinical practice. Similarly, these trials will create greater opportunities for enabling a more granular evaluation of patient “phenotypes” who may be more or less likely to benefit from either strategy, along with a better understanding of the resource implications and the natural history for patients with AKI who were enrolled but did not receive RRT.

Conclusions
Recently completed clinical trials have highlighted the long-standing dilemma of when to optimally start RRT in critically ill patients with AKI. These trials, as well as previous work done in this area, demonstrated that any attempt to protocolize an “early” strategy of RRT initiation will necessarily entail the receipt of RRT by some individuals who, with supportive care and the tincture of time, would recover kidney function without ever needing RRT. In the absence of a reliable clinical tool to predict the need for RRT in the setting of severe AKI, clinician involvement in patient selection is needed to ensure that the trial cohort is enriched by patients who are likely to require RRT at some point during their ICU course. This will require careful consideration of the overall trajectory of the patient, integrating baseline clinical information (i.e., extent of baseline chronic kidney disease), diagnosis, illness acuity, burden of organ dysfunction, along with trends in physiologic and laboratory data, rather than relying on absolute or arbitrary threshold laboratory values (Figure 3). Importantly, clinicians should consider that starting RRT in many patients may be avoidable and in some cases inappropriate given a patient’s or family’s preferences for care or due to the perception of a medical futile prognosis for a patient nearing the end of life, where RRT will clearly not modify outcome. In these circumstances, either a time-limited trial if there is uncertainty or withholding RRT could be aligned with good clinical practice and quality end-of-life care. Additional evidence from ongoing trials will, it is hoped, further inform best clinical practice and work toward the reduction in practice variation in how RRT is initiated.

DISCLOSURE
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REFERENCES


