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.

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

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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.[1,16] 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

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

Absolute indications (in the absence of contraindications to RRT)	• Refractory hyperkalemia (e.g., K^+ >6.5 mmol/l, rapidly increasing, or cardiac toxicity) • Refractory acidemia and metabolic acidosis (e.g., pH ≤7.2 despite normal or low arterial pCO_2) • Refractory pulmonary edema due to fluid overload (i.e., diuretic resistant) • Symptoms or complications attributable to uremia (e.g., bleeding, pericarditis, encephalopathy) • Overdose/toxicity from a dialyzable drug/toxin
Relative indications (in the absence of life-threatening complications of AKI)	• Limited physiologic reserve to tolerate the consequences of AKI • Advanced nonrenal organ dysfunction worsened or exacerbated by excessive fluid accumulation (i.e., impaired respiratory function) • Anticipated solute burden (i.e., tumor lysis syndrome, rhabdomyolysis, intravascular hemolysis) • Need for large volume fluid administration (i.e., nutritional support, medications, or blood products) • Severity of the underlying disease • Concomitant accumulation of poisons or toxic drugs that can be removed by RRT (i.e., salicylates, ethylene glycol, methanol, metformin)
Relative contraindications	• Futile prognosis • Patient receiving palliative care • High likelihood of nonrecovery of renal function in patient who is not a candidate for long-term dialysis

AKI, acute kidney injury; CKD, chronic kidney disease; RRT, renal replacement therapy.
Adapted from Papazian L, Forel JM, Gacouin A, et al. (Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med*. 2010;363:1107–1116).[61]

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

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

AKI, acute kidney injury; RRT, renal replacement therapy.
Adapted from Papazian L, Forel JM, Gacouin A, et al. (Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med*. 2010;363:1107–1116).[61]

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.[36] 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.[37] 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, Conger[43] 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,

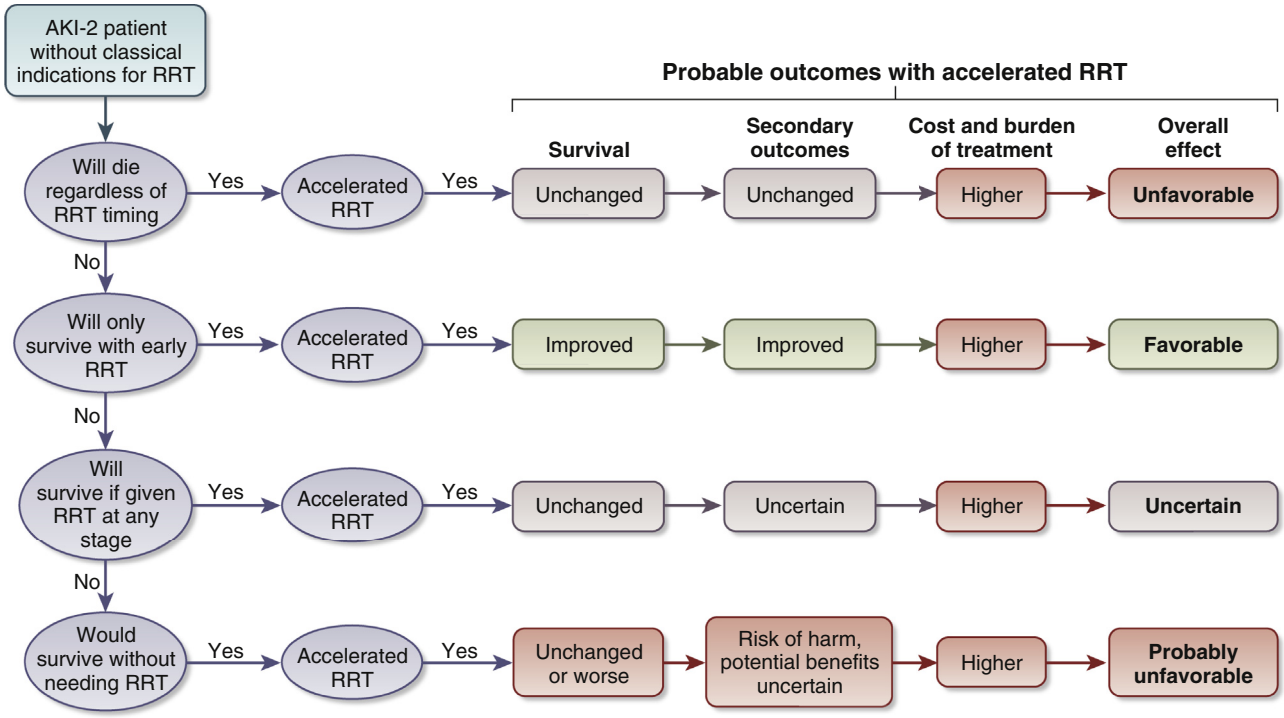

Figure 1 | Potential impact of heterogeneity of treatment effect and practice misalignment on outcome in a trial of timing of starting renal replacement therapy (RRT) in critically ill patients with acute kidney injury (AKI). Reproduced with permission from Prowle JR, Davenport A. Does early-start renal replacement therapy improve outcomes for patients with acute kidney injury? *Kidney Int*. 2015;88:670–673.[68] Copyright © 2015, International Society of Nephrology.

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.[15] 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.[37]

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

Organization	Recommendations
Kidney Disease: Improving Global Outcomes (KDIGO)[24]	(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)[25]	(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)[58]	(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.[57] 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.*[53] 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 completed[56] (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 4 | Summary of previous completed randomized, controlled trials investigating the timing of RRT

Study	Time period	Size	RRT modality	Patient population	Intervention		Outcome (early RRT vs. control)	Additional comments
					Early RRT	Control		
Conger[43]	Vietnam War (pre-1975)	$N = 18$ SC	IHD	Adult, major trauma	Urea >17.8 mmol/l or SCr >442 μmol/l	Urea >42.8 mmol/l or SCr >884 μmol/l	Mortality: 38% versus 80%	-
Pursnani *et al.*[58]	N/A	$N = 35$ SC	IHD	Adult medical/ obstetric	Urea >42.8 mmol/l or SCr >619 μmol/l	Clinical decision	Mortality: 22% versus 29%	↓ Complications and hospital stay in early RRT
Sugahara and Suzuki[50]	1995–1997	$N = 28$ SC	PIRRT	Adult cardiac surgery	UO <30 ml/h × 3 h and SCr <44 μmol/l per d	UO <20 ml/h × 2 h and SCr >44 μmol/l per day	Mortality (14 d): 14% versus 86% ($P < 0.01$)	2 patients in "early" group were still on RRT at day 14
Durmaz *et al.*[49]	1999–2001	$N = 44$ SC	IHD	Adult CKD, cardiac surgery	10% ↑ SCr from preoperative value	≥50% increase in SCr or UO <400 ml/24 h	Mortality: 5% versus 30% ($P = 0.048$)	↓ Complications and ICU stay in early RRT
Bouman *et al.*[53]	1998–2000	$N = 106$, 2 centers	CVVH	Adult, critically ill, shock	UO <30 ml/h × 6 h and CrCl <20 ml/min	Urea >40 mmol/l or K^+ >6.5 mmol/l or pulmonary edema	Mortality (28 d): 29% versus 25% ($P = 0.8$) Recovery: no difference	4 patients in control recovered before RRT was started
Jamale *et al.*[55]	2011–2012	$N = 208$ SC	IHD	Adult community-acquired AKI	Urea >25 mmol/l and/or SCr >619 μmol/l	Conventional indication for RRT (per consensus decision by 2 nephrologists)	Mortality (hospital): 21% versus 12% ($P = 0.2$) DD (3 mo): 5% versus 5%	13% recovered kidney function and 12% received emergency RRT in control
STARRT-AKI pilot[56]	2012–2014	$N = 100$ MC	Mixed	Adult critically ill	Two of: SCr >2× baseline; UO <6 ml/kg × 12 h; blood NGAL >400 ng/ml	Conventional indicator for RRT	Mortality (90 d): 38% versus 37% DD (90 d): 0% versus 6%	Trial design proven feasible

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.

Table 5 | Summary of recently completed and ongoing randomized clinical trials evaluating the optimal timing of initiation of RRT in ICU settings

Feature	ELAIN[51]	AKIKI[54]	IDEAL-ICU[66]	STARRT-AKI
Country	Germany	France	France	Canada
No. of sites	1	31	24	>60
No. of participants	231	620	864[a]	2866[a]
Setting/population	Mixed medical/ surgical ICU (94.8% surgical)	Mixed medical/ surgical ICU (79.7% medical)	Mixed medical/ surgical ICU (septic shock)	Mixed medical/ surgical ICU
ARR for sample size calculation	18%	15%	10%	6%
Control group mortality	55%	55%	55%	40%
Interventions				
Early	KDIGO stage 2 (within 8 h)	KDIGO stage 3 (within 6 h)	KDIGO stage 3[b] (within 12 h)	KDIGO stage 2 (within 12 h)
Delayed (conservative)	KDIGO stage 3 (within 12 h)	Specific criteria/emergent indications	Specific criteria 48–60 h after eligibility or emergent indications	Specific criteria/emergent indications
Time difference	25.5 h	57.0 h	N/A	41.6 h[c]
Received RRT in delayed	90.8%	51.0%	N/A	N/A
RRT modality	Continuous RRT	Physician discretion (initial IHD 55%)	Physician discretion	Physician discretion
SOFA score of enrolled patient	~16.0	~10.9	N/A	N/A
Primary endpoint	90-d mortality	60-d mortality	90-d mortality	90-d mortality
Early	39.3%	48.5%	N/A	N/A
Delayed	54.7%	49.7%	N/A	N/A

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.
[a]Planned enrollment.
[b]IDEAL-ICU protocol utilizes the RIFLE classification for AKI. RIFLE-F generally aligns with KDIGO stage 3.
[c]Based on STARRT-AKI pilot data.

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)[51] (Table 5). Eligible patients were required to have plasma neutrophil gelatinase-associated lipocalin >150 ng/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 ng/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[54] (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

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.[59–61] 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 (RENAL) 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,[57] 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 trial[62] (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.[46,63–65]

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.

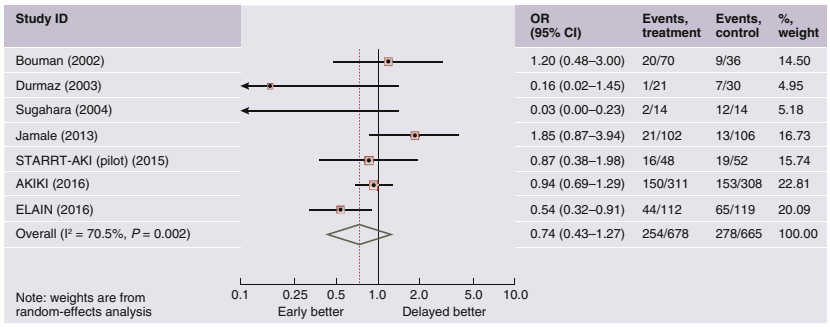

Figure 2 | Forest plot of recently completed randomized clinical trials of the timing of initiation of renal replacement therapy (RRT) focused on critically ill patients with acute kidney injury (AKI). Pooled effect estimate, odds ratio (OR), 95% confidence interval (CI), of early compared with delayed or late RRT initiation on mortality (however defined by the study). Studies included were recently completed (after year 2000) randomized trials focused on critically ill patients with confirmed AKI.

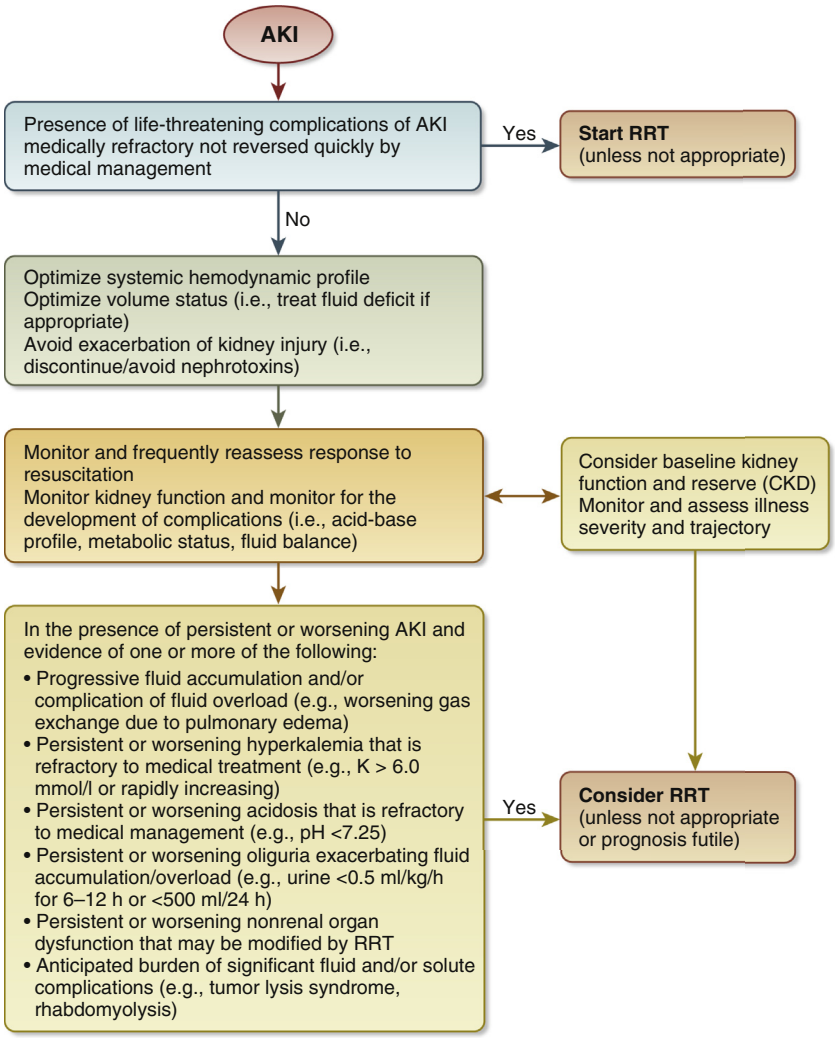

Figure 3 | Proposed algorithm for initiation renal replacement therapy (RRT) in critically ill patients with acute kidney injury (AKI). CKD, chronic kidney disease. Adapted with permission from Ostermann M, Wald R, Bagshaw SM. Timing of renal replacement therapy in acute kidney injury. *Contrib Nephrol.* 2016;187:106–120.[21] Copyright © 2016, S. Karger AG.

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).[66] 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 ≥6.0 mmol/l, pH ≤7.20 or serum bicarbonate ≤12 mmol/l, evidence of severe hypoxemia (Pa_{O_2}/Fi_{O_2} ≤200) attributable to fluid overload, or persistence of AKI for 72 hours. The primary

endpoint is 90-day mortality. A recently published 100-patient multicenter pilot trial highlighted the feasibility of executing the STARRT-AKI protocol.[56]

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.[67] 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

1. Hoste EA, Bagshaw SM, Bellomo R, et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. *Intensive Care Med*. 2015;41:1411–1423.
2. Mehta RL, Burdman EA, Cerdá J, et al. Recognition and management of acute kidney injury in the International Society of Nephrology 0by25 Global Snapshot: a multinational cross-sectional study. *Lancet*. 2016;387:2017–2025.
3. Yang L, Xing G, Wang Wu Y, et al. Acute kidney injury in China: a cross-sectional survey. *Lancet*. 2015;386:1465–1471.
4. Chawla LS, Amdur RL, Amodeo S, et al. The severity of acute kidney injury predicts progression to chronic kidney disease. *Kidney Int*. 2011;79:1361–1369.
5. Chawla LS, Amdur RL, Shaw AD, et al. Association between AKI and long-term renal and cardiovascular outcomes in United States veterans. *Clin J Am Soc Nephrol*. 2014;9:448–456.
6. Wu VC, Wu CH, Huang TM, et al. Long-term risk of coronary events after AKI. *J Am Soc Nephrol*. 2014;25:595–605.
7. Wu VC, Wu PC, Wu CH, et al. The impact of acute kidney injury on the long-term risk of stroke. *J Am Heart Assoc*. 2014; Jul 15;3(4).
8. Lai TS, Wang CY, Pan SC, et al. Risk of developing severe sepsis after acute kidney injury: a population-based cohort study. *Crit Care*. 2013;17:R231.
9. Mehta RL, Bouchard J, Soroko SB, et al. Sepsis as a cause and consequence of acute kidney injury: Program to Improve Care in Acute Renal Disease. *Intensive Care Med*. 2011;37:241–248.
10. Yang WS, Hu FC, Chen MK, et al. High risk of herpes zoster among patients with advance acute kidney injury–a population-based study. *Sci Rep*. 2015;5:13747.
11. Wu PC, Wu CJ, Lin CJ, Wu VC, National Taiwan University Study Group on Acute Renal Failure Group. Long-term risk of upper gastrointestinal hemorrhage after advanced AKI. *Clin J Am Soc Nephrol*. 2015;10:353–362.
12. Chao CT, Wang CY, Lai CF, et al. Dialysis-requiring acute kidney injury increases risk of long-term malignancy: a population-based study. *J Cancer Res Clin Oncol*. 2014;140:613–621.
13. Wang WJ, Chao CT, Huang YC, et al. The impact of acute kidney injury with temporary dialysis on the risk of fracture. *J Bone Miner Res*. 2014;29:676–684.
14. Vaara ST, Pettilä V, Kaukonen KM, et al. The attributable mortality of acute kidney injury: a sequentially matched analysis*. *Crit Care Med*. 2014;42:878–885.
15. Liborio AB, Leite TT, Neves FM, et al. AKI complications in critically ill patients: association with mortality rates and RRT. *Clin J Am Soc Nephrol*. 2015;10:21–28.
16. Nisula S, Kaukonen KM, Vaara ST, et al. Incidence, risk factors and 90-day mortality of patients with acute kidney injury in Finnish intensive care units: the FINNAKI study. *Intensive Care Med*. 2013;39:420–428.
17. Hsu RK, McCulloch CE, Dudley RA, et al. Temporal changes in incidence of dialysis-requiring AKI. *J Am Soc Nephrol*. 2013;24:37–42.
18. Kolhe NV, Muirhead AW, Wilkes SR, et al. National trends in acute kidney injury requiring dialysis in England between 1998 and 2013. *Kidney Int*. 2015;88:1161–1169.
19. Wald R, McArthur E, Adhikari NK, et al. Changing incidence and outcomes following dialysis-requiring acute kidney injury among critically ill adults: a population-based cohort study. *Am J Kidney Dis*. 2015;65:870–877.
20. Parsons FM, Hobson SM, Blagg CR, McCracken BH. Optimum time for dialysis in acute reversible renal failure. Description and value of an improved dialyser with large surface area. *Lancet*. 1961;1:129–134.
21. Ostermann M, Wald R, Bagshaw SM. Timing of renal replacement therapy in acute kidney injury. *Contrib Nephrol*. 2016;187:106–120.
22. Wald R, Bagshaw SM. The timing of renal replacement therapy initiation in acute kidney injury. *Semin Nephrol*. 2016;36:78–84.
23. Joannidis M, Forni LG. Clinical review: timing of renal replacement therapy. *Crit Care*. 2011;15:223.
24. Kidney Disease Improving Global Outcome. KDIGO Clinical Practice Guideline for Acute Kidney Injury. (2012). Available at: http://kdigo.org/home/guidelines/acute-kidney-injury/. Accessed July 9, 2016.

25. National Institute for Health and Care Excellence (NICE). Acute kidney injury: prevention, detection and management. (2013). Available at: https://www.nice.org.uk/guidance/cg169/. Accessed July 9, 2016.
26. Bagshaw SM, Wald R, Barton J, et al. Clinical factors associated with initiation of renal replacement therapy in critically ill patients with acute kidney injury-a prospective multicenter observational study. *J Crit Care*. 2012;27:268–275.
27. Clark E, Wald R, Levin A, et al. Timing the initiation of renal replacement therapy for acute kidney injury in Canadian intensive care units: a multicentre observational study. *Can J Anaesth*. 2012;59:861–870.
28. Clark E, Wald R, Walsh M, Bagshaw SM, Canadian Acute Kidney Injury, I. Timing of initiation of renal replacement therapy for acute kidney injury: a survey of nephrologists and intensivists in Canada. *Nephrol Dial Transplant*. 2012;27:2761–2767.
29. Elseviers MM, Lins RL, Van der Niepen P, et al. Renal replacement therapy is an independent risk factor for mortality in critically ill patients with acute kidney injury. *Crit Care*. 2010;14:R221.
30. Gaudry S, Ricard JD, Leclaire C, et al. Acute kidney injury in critical care: experience of a conservative strategy. *J Crit Care*. 2014;29:1022–1027.
31. Hsu RK, McCulloch CE, Ku E, et al. Regional variation in the incidence of dialysis-requiring AKI in the United States. *Clin J Am Soc Nephrol*. 2013;8:1476–1481.
32. Srisawat N, Sileanu FE, Murugan R, et al. Variation in risk and mortality of acute kidney injury in critically ill patients: a multicenter study. *Am J Nephrol*. 2015;41:81–88.
33. Clec'h C, Darmon M, Lautrette A, et al. Efficacy of renal replacement therapy in critically ill patients: a propensity analysis. *Crit Care*. 2012;16:R236.
34. Guerin C, Girard R, Selli JM, et al. Initial versus delayed acute renal failure in the intensive care unit. A multicenter prospective epidemiological study. Rhone-Alpes Area Study Group on Acute Renal Failure. *Am J Respir Crit Care Med*. 2000;161:872–879.
35. Bagshaw SM, Uchino S, Kellum JA, et al. Association between renal replacement therapy in critically ill patients with severe acute kidney injury and mortality. *J Crit Care*. 2013;28:1011–1018.
36. Kawarazaki H, Uchino S, Tokuhira N, et al. Who may not benefit from continuous renal replacement therapy in acute kidney injury? *Hemodial Int*. 2013;17:624–632.
37. Clark EG, Bagshaw SM. Unnecessary renal replacement therapy for acute kidney injury is harmful for renal recovery. *Semin Dial*. 2015;28:6–11.
38. Vaara ST, Reinikainen M, Wald R, et al. Timing of RRT based on the presence of conventional indications. *Clin J Am Soc Nephrol*. 2014;9:1577–1585.
39. Karvellas CJ, Farhat MR, Sajjid I, et al. A comparison of early versus late initiation of renal replacement therapy in critically ill patients with acute kidney injury: a systematic review and meta-analysis. *Crit Care*. 2011;15:R72.
40. Wang X, Jie Yuan W. Timing of initiation of renal replacement therapy in acute kidney injury: a systematic review and meta-analysis. *Ren Fail*. 2012;34:396–402.
41. Wierstra BT, Kadri S, Alomar S, et al. The impact of "early" versus "late" initiation of renal replacement therapy in critical care patients with acute kidney injury: a systematic review and evidence synthesis. *Crit Care*. 2016;20:122.
42. Liu Y, Davari-Farid S, Arora P, et al. Early versus late initiation of renal replacement therapy in critically ill patients with acute kidney injury after cardiac surgery: a systematic review and meta-analysis. *J Cardiothorac Vasc Anesth*. 2014;28:557–563.
43. Conger JD. A controlled evaluation of prophylactic dialysis in post-traumatic acute renal failure. *J Trauma*. 1975;15:1056–1063.
44. Gettings LG, Reynolds HN, Scalea T. Outcome in post-traumatic acute renal failure when continuous renal replacement therapy is applied early vs. late. *Intensive Care Med*. 1999;25:805–813.
45. Teschan PE, Baxter CR, O'Brien TF, et al. Prophylactic hemodialysis in the treatment of acute renal failure. *Ann Intern Med*. 1960;53:992–1016.
46. Bagshaw SM, Wald R. Acute kidney injury: timing of renal replacement therapy in AKI. *Nat Rev Nephrol*. 2016;12:445–446.
47. Combes A, Bréchot N, Amour J, et al. Early High-Volume Hemofiltration versus Standard Care for Post-Cardiac Surgery Shock. The HEROICS Study. *Am J Respir Crit Care Med*. 2015;192:1179–1190.
48. Payen D, Mateo J, Cavaillon JM, et al. Impact of continuous venovenous hemofiltration on organ failure during the early phase of severe sepsis: a randomized controlled trial. *Crit Care Med*. 2009;37:803–810.
49. Durmaz I, Yaqdi T, Calkavur T, et al. Prophylactic dialysis in patients with renal dysfunction undergoing on-pump coronary artery bypass surgery. *Ann Thorac Surg*. 2003;75:859–864.
50. Sugahara S, Suzuki H. Early start on continuous hemodialysis therapy improves survival rate in patients with acute renal failure following coronary bypass surgery. *Hemodial Int*. 2004;8:320–325.
51. Zarbock A, Kellum JA, Schmidt C, et al. Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: the ELAIN Randomized Clinical Trial. *JAMA*. 2016;315:2190–2199.
52. Augustine JJ, Sandy D, Seifert TH, Paganini EP. A randomized controlled trial comparing intermittent with continuous dialysis in patients with ARF. *Am J Kidney Dis*. 2004;44:1000–1007.
53. Bouman CS, Oudemans-Van Straaten HM, Tijssen JG, et al. Effects of early high-volume continuous venovenous hemofiltration on survival and recovery of renal function in intensive care patients with acute renal failure: a prospective, randomized trial. *Crit Care Med*. 2002;30:2205–2211.
54. Gaudry S, Hajage D, Schortgen F, et al. Initiation strategies for renal-replacement therapy in the intensive care unit. *N Engl J Med*. 2016;375:122–133.
55. Jamale TE, Hase NK, Kulkami M, et al. Earlier-start versus usual-start dialysis in patients with community-acquired acute kidney injury: a randomized controlled trial. *Am J Kidney Dis*. 2013;62:1116–1121.
56. Wald R, Adhikari NK, Smith OM, et al. Comparison of standard and accelerated initiation of renal replacement therapy in acute kidney injury. *Kidney Int*. 2015;88:897–904.
57. Pursnani NM, Hazra DK, Singh B, et al. Early haemodialysis in acute tubular necrosis. *J Assoc Physicians India*. 1997;45:850–852.
58. Vinsonneau C, Allian-Launay E, Blayau C, et al. Renal replacement therapy in adult and pediatric intensive care: Recommendations by an expert panel from the French Intensive Care Society (SRLF) with the French Society of Anesthesia Intensive Care (SFAR) French Group for Pediatric Intensive Care Emergencies (GFRUP) the French Dialysis Society (SFD). *Ann Intensive Care*. 2015;5:58.
59. Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med*. 2000;342:1301–1308.
60. Guerin C, Reignier J, Richard JC. Prone positioning in the acute respiratory distress syndrome. *N Engl J Med*. 2013;369:980–981.
61. Papazian L, Forel JM, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med*. 2010;363:1107–1116.
62. Deans KJ, Minneci PC, Suffredini AF, et al. Randomization in clinical trials of titrated therapies: unintended consequences of using fixed treatment protocols. *Crit Care Med*. 2007;35:1509–1516.
63. Bagshaw SM, Lamontagne F, Joannidis M, Wald R. When to start renal replacement therapy in critically ill patients with acute kidney injury: comment on AKIKI and ELAIN. *Crit Care*. 2016;20:245.
64. Chertow GM, Winkelmayer WC. Early to Dialyze: Healthy and Wise? *JAMA*. 2016;315:2171–2172.
65. Mehta RL. Renal-Replacement Therapy in the Critically Ill–Does Timing Matter? *N Engl J Med*. 2016;375:175–176.
66. Barbar SD, Binquet C, Monchi M, et al. Impact on mortality of the timing of renal replacement therapy in patients with severe acute kidney injury in septic shock: the IDEAL-ICU study (initiation of dialysis early versus delayed in the intensive care unit): study protocol for a randomized controlled trial. *Trials*. 2014;15:270.
67. Gabbay E, Meyer KB. Identifying critically ill patients with acute kidney injury for whom renal replacement therapy is inappropriate: an exercise in futility? *NDT Plus*. 2009;2:97–103.
68. Prowle JR, Davenport A. Does early-start renal replacement therapy improve outcomes for patients with acute kidney injury? *Kidney Int*. 2015;88:670–673.