Timing of Renal Replacement Therapy for Severe Acute Kidney Injury in Critically Ill Patients

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Abstract

Acute kidney injury (AKI) affects many ICU patients and is responsible for increased morbidity and mortality. Although lifesaving in many situations, renal replacement therapy (RRT) may be associated with complications, and the appropriate timing of its initiation is still the subject of intense debate. An early initiation strategy can prevent some metabolic complications, whereas a delayed one may allow for renal function recovery in some patients without need for this costly and potentially dangerous technique. For years, most of the knowledge on this issue stemmed from observational studies or small randomized controlled trials. Recent randomized controlled trials have indicated that a watchful waiting strategy (in the absence of life-threatening conditions such as severe hyperkalemia or pulmonary edema) during severe AKI allowed many patients to escape RRT and did not seem to adversely affect survival compared with a strategy of immediate RRT. In addition, data suggest that a delayed strategy may reduce the rate of complications (such as catheter infection) and favor renal function recovery. Ongoing studies will have to both confirm these conclusions and clarify to what extent the delay in initiating RRT can be prolonged. Pending those results, the bulk of evidence suggests that, in the absence of potential severe complications of AKI, delaying RRT is a valid and safe strategy that may also allow for considerable cost savings.

Keywords: acute kidney injury; renal replacement therapy; renal function recovery

Approximately half of ICU patients are affected by acute kidney injury (AKI) either upon admission or during their stay (1, 2). AKI is associated with both increased mortality (3) and long-term sequelae such as chronic kidney disease (CKD) (3). The treatment of AKI is based on both conservative measures (medical treatment of hyperkalemia and of fluid overload, for instance) and timely use of renal replacement therapy (RRT). The latter was invented more than 70 years ago and saved many lives (4), but its timing remains a subject of intense debate (5). Earlier studies addressed patients who died of complications that are now infrequent during AKI. For instance, the incidence of acquired digestive bleeding and bacteremia accounted for 24% and 29% of deaths, respectively (6). So-called prophylactic use of RRT allowed considerable reduction of these complications (6). However, this "prophylactic" RRT was implemented at rather late stages of AKI with plasma urea concentration reaching 33–50 mmol/L (4, 6) and would be considered nowadays as a "late" initiation. The pattern of AKI has

(Received in original form October 11, 2018; accepted in final form February 20, 2019)

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Author Contributions: Conception, design, and drafting of the manuscript: all authors.

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Am J Respir Crit Care Med Vol 199, Iss 9, pp 1066–1075, May 1, 2019

Originally Published in Press as DOI: 10.1164/rccm.201810-1906CP on February 20, 2019
Internet address: www.atsjournals.org

changed since these early studies, and this condition is now associated with other organ failures, such as acute respiratory distress syndrome (ARDS) or septic shock, in most instances (7–9). Tremendous progress in the management of these latter conditions has allowed for dramatic mortality reduction (10) and masks any putative change of AKI prognosis with time. Therefore, older studies on RRT initiation as well as meta-analyses including such studies are outdated with regard to information on the optimal timing for RRT initiation in the modern critical care era.

This critical care perspective article deals with the timing of RRT during AKI and does not address the problem of RRT for drug or poison removal. Of note, it was written by authors of the only two large randomized controlled trials (RCTs) on RRT initiation strategies that were recently published (AKIKI [Artificial Kidney Initiation in Kidney Injury] [7] and IDEAL-ICU [Initiation of Dialysis Early versus Delayed in Intensive Care Unit] [9]). Interestingly, the starting hypotheses of these two RCTs were strictly opposite: The AKIKI study postulated increased survival with a delayed RRT initiation strategy, whereas the IDEAL-ICU study postulated increased survival with an early RRT initiation strategy. The results of the two studies were concordant (and invalidated both hypotheses) because they did not show a survival difference according to strategy.

Prerequisite for Research on RRT

Two kinds of issues must be addressed: RRT techniques and timing of RRT initiation. Research initially focused on modalities, and no obvious difference in outcome was evidenced according to the site (jugular or femoral [11, 12]) of catheter insertion, the modality of RRT (continuous or intermittent [13, 14]), or the intensity of RRT (15–17), provided these were adapted to the special condition of critically ill patients (18).

In contrast with numerous large RCTs on RRT modalities, most data on RRT timing was derived, until recently, from observational studies and small RCTs. Observational studies have a low grade of evidence and are irredeemably flawed by the fact that they, by design, compared patients who all actually received RRT, be it called "early" or "late," thereby omitting the possibility that many patients might recover without ever receiving RRT and have an excellent prognosis (19–21). The few available RCTs were conducted before the progress mentioned in the introductory text above and involved small numbers of patients. It therefore comes as no surprise that meta-analyses published 10 years ago claimed the superiority of "early" over "delayed" RRT (22, 23), because they were affected by numerous confounding factors (discussed below). A fertile field was left open for studies comparing strategies and not timing, therefore allowing some patients to escape RRT (21).

An Overview of Guidelines before RCTs Were Available

Given the critical dearth of evidence-based recommendations, clinicians relied on expert opinion and common wisdom for years (24–26). Absolute indications for RRT included the following:

- Hyperkalemia (>6 mmol/L with ECG abnormalities).
- Fluid overload resistant to diuretic administration.
- Severe metabolic acidosis (pH, <7.15).
- Blood urea concentration greater than 35.7 mmol/L. This threshold was not supported by data (27), because high degrees of uremia may be well tolerated (provided they are not associated with neurological impairment). As a matter of fact, median blood urea concentration was 39 mmol/L (with extremes as high as 67 mmol/L [S. Gaudry and colleagues, unpublished results]) in a study reporting a conservative strategy of RRT initiation (28).

Guidelines specified that in the absence of life-threatening conditions, RRT could be delayed (25, 26). However, these recommendations were seldom followed, and many intensivists based their decisions on values of both urine output and urea/creatinine concentrations (29). These uncertainties and practice heterogeneity made large RCTs on RRT timing a top priority (25, 30).

Clinical Equipoise Warranted Implementation of RCTs

Theoretical arguments may support early RRT initiation: better control of fluid balance, electrolyte abnormalities (even in the absence of life-threatening condition such as severe hyperkalemia), and acid–base status. In addition, limiting the rise of potential toxins produced by protein catabolism (reflected by the concentrations of blood urea nitrogen [BUN] and serum creatinine) might prove beneficial. An early initiation of RRT might also decrease the risk of bleeding related to platelet dysfunction due to uremia and prevent the onset of uremic encephalopathy. Regarding the latter, one must bear in mind, however, that uremic encephalopathy is difficult to diagnose in critically ill patients in the setting of encephalopathy resulting from sepsis and other critical illnesses, use of sedatives and opiate analgesics, and frequent occurrence of delirium. Removal of inflammatory cytokines (allowing modulation of the immune system response) by RRT during sepsis has also been considered as an argument for early initiation (31–33). Experimental studies indeed showed that high-volume hemofiltration improved myocardial performance and systemic hemodynamics while removing inflammatory cytokines (34–38). However, no clinical counterpart for this interesting hypothesis was proven in human studies, hemofiltration having failed to decrease plasma cytokine concentration and to improve organ dysfunction during sepsis and septic shock (39). Moreover, high-volume and very high–volume hemofiltration did not improve patient survival (40, 41).

Alternatively, RRT is not devoid of risk (e.g., catheter insertion–related complications, catheter-related bloodstream infections and thrombosis, dialytic hypotension, hypophosphatemia, and hypokalemia, among others) (42). Although the use of more biocompatible dialysis membranes considerably improved RRT safety (43), interaction between blood and artificial membranes may trigger cellular and humoral mechanisms of inflammation.

In addition, pathophysiology of tubular lesions and repair should be considered. Proximal tubules are located in the corticomedullary junction of renal parenchyma, where Pa_{O_2} is physiologically below 40 mm Hg, and are therefore highly susceptible to any kind of injury, including RRT-related complications, which may constitute a second hit on an injured

tubular epithelium. Interestingly, immediate postmortem renal "biopsy" of ICU patients dying with AKI revealed more severe tubular lesions in those who had been subjected to RRT (44). Rapid tubular repair usually allows for renal function recovery in a couple of weeks. Nevertheless, unexpected discoveries were made in the last decade, as discussed below.

First, the risk of developing CKD after AKI is increased several-fold in the first years or even months after the initial injury (45). Interestingly, in wild-type mice subjected to a nonlethal model of ischemic AKI, a second injury was found to hasten renal fibrogenesis (46). Avoiding any superimposed injury is therefore of paramount importance during the course of AKI.

Second, necrotic tubules are replaced by surviving tubular cells themselves and not by renal or extrarenal "stem" cells (47). This implies that the repairing epithelium has also been exposed to injury. It may thus exhibit metabolic and cell-cycle defects that have been shown to promote fibrosis in the long term (48). The impact of RRT at this sensitive phase of epithelial repair is unknown, but removal of beneficial blood components might impede renal function recovery and long-term prognosis. For instance, the nicotinamide adenine dinucleotide (NAD) metabolic pathway plays an important role in the recovery of AKI in mouse ischemic AKI (49). Moreover, AKI results in renal NAD content decrease in mice (50), potentially making kidneys more susceptible to further injury. Interestingly, a human counterpart of the deleterious effect of renal NAD depletion was demonstrated in patients with post–cardiac surgery AKI (50). NAD can be synthesized *de novo* from dietary tryptophan or from a salvage route using dietary niacin (vitamin B_3 or PP). Plasma kynurenine, an intermediate metabolite essential to the *de novo* pathway, is reduced by roughly 50% during hemodialysis (51). This is a serious concern because genetic depletion of this pathway aggravates ischemic AKI in murine models (49). The molecular weight of niacin is 122 Da, very close to that of creatinine (113 Da), making it very likely to be removed by RRT and raising the possibility that NAD synthesis may be severely compromised by RRT. Giving vitamin B_3 as an agent to promote the rescue pathway has been shown to protect from human AKI after cardiac surgery in a phase I study (50). Larger studies are required to test the potential beneficial effect of niacin supplementation on the prevention and/or course of human AKI.

All this suggests that in patients with resolving ischemic AKI, the kidneys are somehow sensitized to a harmful environment and may develop what is now called a "maladaptive repair" (52) in case another aggression occurs (53). Altogether, the risk of starting RRT at a time when renal tubular epithelial tissue begins to repair must be carefully balanced against the putative benefits of this technique. Performing RCTs on the timing of RRT obviously fulfills the criteria for equipoise (54).

Analysis of Recent RCTs

The first bicentric RCT on RRT timing (55) involved 106 critically ill patients (predominantly after cardiac surgery) randomly allocated to one of three groups: two early-RRT groups (high- or low-volume hemofiltration) and one late-RRT group (low-volume hemofiltration). Criteria for RRT initiation in the late group were plasma urea concentration greater than 40 mmol/L, hyperkalemia greater than 6.5 mmol/L, and severe pulmonary edema. Survival and renal function recovery were not improved by early RRT initiation (whatever the volume of hemofiltration). Although underpowered, this study provided an indication of the safety of delaying RRT.

Table 1 summarizes results of more recent studies. The first large-scale RCT included 208 patients with community-acquired AKI treated outside an ICU at a single center in India (56). Critically ill patients (shock present in 25% and Sequential Organ Failure Assessment [SOFA] score of 8 on admission) were randomized to an early strategy (RRT started once serum urea or creatinine concentration exceeded 25 mmol/L or 619 mmol/L, respectively) or to a delayed strategy (RRT started only in the context of refractory hyperkalemia, volume overload, acidosis or uremic nausea, and anorexia). Hospital mortality was low with both strategies, particularly in the "delayed" one (12.2% [delayed strategy] vs. 20.5% [early strategy]; $P = 0.2$), in which 17% did not receive RRT. It may be difficult to extrapolate these findings to countries with widespread ICU facilities, but they constitute a strong argument in favor of the safety of a delayed RRT strategy.

More recently, the ELAIN (Early versus Late Initiation of Renal Replacement Therapy in Critically Ill Patients with Acute Kidney Injury) study (57) was conducted in 231 postsurgical (mainly cardiac surgery) patients in a single center and reported an advantage of an early strategy. RRT initiation depended on Kidney Disease: Improving Global Outcomes (KDIGO) stage but not on complications (contrary to the vast majority of RCTs on the timing of RRT). Early and delayed groups received RRT when they reached KDIGO 2 and KDIGO 3, respectively. Other inclusion criteria included at least one of the following: severe sepsis, use of vasopressors, refractory fluid overload (worsening pulmonary edema, Pa_{O2}/Fi_{O2} <300 mm Hg, or fluid balance $>10\%$ of body weight), or development or progression of nonrenal organ dysfunction (SOFA score ≥ 2). Finally, almost 75% of patients had refractory fluid overload criteria (including worsening pulmonary edema) at baseline but were nevertheless randomized to immediate or delayed RRT initiation. More than 90% of KDIGO 2 patients reached stage 3 and received RRT. In that sense, the ELAIN trial contrasts with observational studies which show that less than one-half of critically ill patients with equivalent stage 2 progress to stage 3 AKI (58). The median (interquartile range) delay in RRT between groups was only 21 (18–24) hours. Such a small difference in RRT initiation delay surprisingly resulted in a significant difference in 90-day mortality in favor of the early strategy (49 of 112 [39%] vs. 65 of 119 [55%]; $P = 0.03$). Moreover, early RRT initiation was associated with considerable reductions in median duration of both RRT (>2 wk) and hospital stay (>4 wk, an amazing difference in an RCT performed in an ICU). These intriguing features were underlined in a recent editorial by Liu and Palevsky (59). Difference in mortality was observed not at Day 60, but at Day 90 only, a finding difficult to explain in the ICU setting. The low fragility index (60) (of three patients only) may attest to the fact that single-center studies often overestimate the effect of the experimental arm (61). Most authorities (as well as

Table 1. Recent Randomized Controlled Trials on the Timing of Renal Replacement Therapy Initiation during Acute Kidney Injury

	Jamale *et al.*, 2013 (56)	STARRT-AKI Pilot Study, 2013 (74)	ELAIN Study, 2016 (57)	AKIKI Study, 2016 (7)	IDEAL-ICU Study, 2018 (9)
Design	Single-center medical ward	Multicenter mixed ICU	Single-center surgical ICU	Multicenter mixed ICU	Multicenter mixed ICU
Patients, *n*	208	100	231	620	488
Early strategy	• Serum urea concentration >25 mmol/L or • Serum creatinine concentration >619 μmol/L	• Serum creatinine ⩾100 μmol/L in women and ⩾130 μmol/L in men • Presence of severe AKI determined by any two of the following: ○ Twofold increase from baseline in serum creatinine ○ Urine output <6 ml/kg in 12 h ○ Whole-blood NGAL ⩾400 ng/ml	• KDIGO stage 2	• KDIGO stage 3	• Failure stage of RIFLE
Inclusion criteria in addition to the presence of AKI	—	—	At least one of the following conditions: • Refractory fluid overload* • Severe sepsis • Catecholamine infusion • Development or progression of nonrenal organ dysfunction	Invasive mechanical ventilation and/or catecholamine infusion	Septic shock
Delayed strategy (criteria for RRT initiation)	• Refractory hyperkalemia • Volume overload • Acidosis • Uremic nausea and anorexia (judged by consensus of two nephrologists)	• Severe hyperkalemia (>6 mmol/L) • Severe acidosis (serum bicarbonate <10 mmol/L) • Severe pulmonary edema (Pa_{O2}/F_{IO2} ratio, <200) refractory to diuretics	• KDIGO stage 3	• Severe hyperkalemia (>6 mmol/L) • Severe pulmonary edema refractory to diuretics • Severe acidosis (pH, <7.15) • Serum urea >40 mmol/L • Oligoanuria >72 h	• Severe hyperkalemia (>6.5 mmol/L) • Severe pulmonary edema refractory to diuretics • Severe metabolic acidosis (pH, <7.15) • No renal function recovery after 48 h
Time difference of RRT initiation between strategies, h	—	24	20	55	45
Percentage of patients free of RRT in the delayed group, %	17	35	9	49	38
Mortality (early vs. delayed RRT), no. of patients					
Day 28	—	18/48 vs. 19/52 ($P = 0.92$)	34/112 vs. 48/119 ($P = 0.11$)	129/311 vs. 134/308 ($P = 0.79$)	111/246 vs. 102/242 ($P = 0.48$)
Day 60	—	—	43/112 vs. 60/119 ($P = 0.07$)	150/311 vs. 153/308 ($P = 0.79$)	—
Day 90	21/102 vs. 13/106 ($P = 0.2$)	—	44/112 vs. 65/119 ($P = 0.03$)	—	138/246 vs. 128/242 ($P = 0.38$)

Definition of abbreviations: AKI = acute kidney injury; AKIKI = Artificial Kidney Initiation in Kidney Injury; ELAIN = Early versus Late Initiation of Renal Replacement Therapy in Critically Ill Patients with Acute Kidney Injury; IDEAL-ICU = Initiation of Dialysis Early versus Delayed in Intensive Care Unit; KDIGO = Kidney Disease: Improving Global Outcomes; NGAL = neutrophil gelatinase-associated lipocalin; RIFLE = risk, injury, failure, loss, and end-stage renal disease; RRT = renal replacement therapy; STARRT-AKI = Standard vs. Accelerated Initiation of RRT in Acute Kidney Injury.

*This inclusion criterion explains the high proportion of patients with fluid overload and pulmonary edema randomized to early or late RRT in the ELAIN trial, whereas severe pulmonary edema was an exclusion criterion in the AKIKI, IDEAL-ICU, and STARRT-AKI (pilot) studies because immediate RRT was mandated.

common wisdom) consider that severe pulmonary edema in an anuric patient is an absolute indication for emergent RRT (25, 26), and, as a matter of fact, Lameire and colleagues underlined that "ELAIN investigated the effect of delaying dialysis in patients who really needed it.… It is thus not surprising that ELAIN concluded that early start improved patient outcome" (62). It is worth mentioning that the same team that published ELAIN is currently conducting a multicenter study on anticoagulation during continuous RRT for AKI, and pulmonary edema is an absolute indication to start RRT in that study (RICH [Regional Citrate versus Systemic Heparin Anticoagulation for Continuous Renal Replacement Therapy in Critically Ill Patients with Acute Kidney Injury] trial; www.clinicaltrials.gov identifier NCT02669589). This seems to indicate that the study authors have drawn appropriate lessons from their previous study.

In addition, ELAIN (which involved only one center) should be put in perspective with a multicenter study, the HEROICS (High Volume Veno-venous Hemofiltration versus Standard Care for Post-cardiac Surgery Shock) trial (63), which included 224 patients with severe shock after cardiac surgery. Indeed, the patient populations were very similar: mostly cardiac surgery patients. Although not all patients had AKI in the HEROICS trial, most probably did because the mean serum creatinine value in HEROICS was 155 μmol/L versus 167 μmol/L in ELAIN. HEROICS showed that a "very early" RRT initiation strategy did not impact mortality compared with a delayed (or standard) RRT initiation, suggesting a potential overestimation of the effect of the experimental arm in the monocentric ELAIN study.

Two recently published large multicenter RCTs (AKIKI and IDEAL-ICU, which involved 620 and 488 patients, respectively) compared early and delayed strategies of RRT (7, 9). Critically ill patients with severe AKI (KDIGO 3 for AKIKI and RIFLE [risk, injury, failure, loss, end-stage renal disease] F for IDEAL-ICU) were allocated to either an immediate or delayed RRT strategy, potentially allowing patients to escape RRT. A high degree of prudence avoided undue risk for patients. Indeed, those with a potentially life-threatening complication (severe and refractory hyperkalemia, severe metabolic acidosis, and severe pulmonary edema due to fluid overload) were not included, because they were considered as urgent indications for RRT. Patients were carefully monitored, and those allocated to the delayed strategy received RRT as soon as a potentially severe complication (defined above) was detected.

There were differences between the two studies. First, contrary to AKIKI, IDEAL-ICU restricted inclusion to patients with sepsis (the AKIKI population, however, comprised 80% of patients with sepsis). Second, the hypotheses of these two RCTs were strictly opposite: AKIKI postulated increased survival with the delayed strategy, whereas IDEAL-ICU postulated increased survival with the early strategy. Third, the AKIKI protocol mandated RRT initiation in the delayed strategy on the basis of prespecified severity criteria (described above), whereas IDEAL-ICU mandated RRT in the delayed arm 48 hours after randomization (or sooner if a complication occurred) even if there was no complication (except in the context of renal recovery). This point underlines the difficulty of defining what a "delayed" strategy is. Such a definition can indeed only be arbitrary, because no one knows how long RRT can be postponed in a patient without any severe complication. In delayed strategies of both studies, RRT was withheld until there was an obvious indication (severe hyperkalemia, among others) or until an arbitrary endpoint was reached, which was 72 hours of oligoanuria or a set value of BUN (112 mg/dl) in AKIKI and 48 hours in IDEAL-ICU. Median delays in RRT initiation after randomization to the early strategy were 2 hours and 2.8 hours in AKIKI and IDEAL-ICU, respectively, whereas these figures were 57 and 48 hours, respectively, in the delayed strategy. This highlights that these two different "arbitrary" definitions resulted in very similar delays and allowed for an important contrast between strategies.

In both studies, the choice of the RRT modality was left at the investigators' discretion. Intermittent hemodialysis was the technique used for the first RRT session in 55% and 44% of patients in AKIKI and IDEAL-ICU, respectively. As mentioned above, the major difference between the two studies resided in their hypotheses. These opposite hypotheses strongly reinforce the plausibility of results of both studies, which did not show any difference in mortality according to the strategy: Mortality was 48% (AKIKI) and 58% (IDEAL-ICU) in the early strategy and 50% and 54% in the delayed one, with P values of 0.79 and 0.38, respectively. Kaplan-Meier survival curves were nearly superposed in both studies (Figure 1), and the minute differences of outcome between early and delayed strategies were in opposite directions. A subgroup analysis of patients with sepsis in AKIKI also showed the absence of significant difference according to strategy (8), in keeping with IDEAL-ICU's findings. Another similarity is that a delayed strategy allowed for a noticeable difference in the number of RRT-free days in surviving patients (17 vs. 19 d in AKIKI, $P < 0.001$; 12 vs. 16 d in IDEAL-ICU, $P = 0.006$). Also, many patients escaped RRT (49% and 38% in AKIKI and IDEAL-ICU, respectively) (Figure 1B). Interestingly, neither of these two studies found any significant difference in terms of fluid balance between early and delayed strategies. The major common conclusion of both studies is that a watchful waiting strategy allowed for considerable reduction of RRT use without any detriment to patients.

In addition, the delayed strategy in AKIKI was associated with significantly fewer catheter-related bloodstream infections and earlier recovery of adequate renal function. A *post hoc* analysis confirmed that mortality in predefined subgroups such as septic shock, ARDS, and tertiles of SOFA and Simplified Acute Physiology Score III scores seemed unaffected by the RRT initiation strategy (8). The same holds true for time to successful extubation in patients with ARDS. Another *post hoc* analysis focusing on 60 patients with CKD (creatinine clearance between 30 and 60 ml/min) showed significant treatment effect heterogeneity according to the CKD status (test for interaction $P = 0.006$). In patients with CKD, the hazard ratio associated with randomization group was 0.40 (95% confidence interval, 0.20–0.81; $P = 0.009$), indicating that the early RRT initiation strategy was strongly associated with increased risk of death after 60 days in this patient population (64). Randomization strategy had no effect in patients without CKD (hazard ratio, 1.13; 95% confidence interval, 0.89–1.44; $P = 0.31$). Obviously,

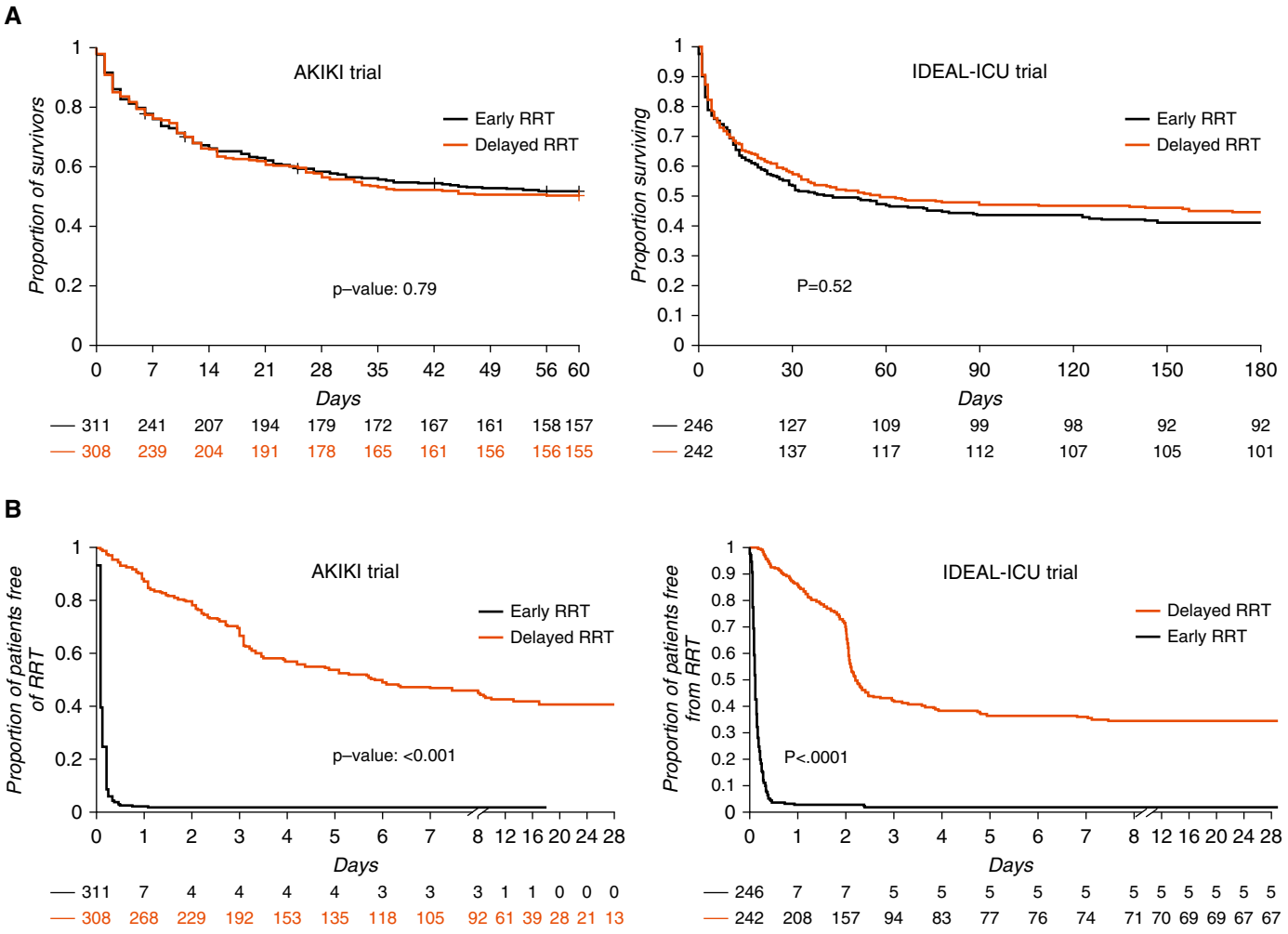

Figure 1. Kaplan-Meier curves of (*A*) the probability of survival and (*B*) the proportion of patients free of renal replacement therapy (RRT), according to RRT strategy in the AKIKI (Artificial Kidney Initiation in Kidney Injury [7]) and IDEAL-ICU (Initiation of Dialysis Early versus Delayed in Intensive Care Unit [9]) studies. Note that curves in *A* are nearly superposed and that the minute differences between early and delayed strategies are in the opposite direction in these studies. Reprinted by permission from References 7 and 9.

this subgroup analysis of patients with CKD is only hypothesis generating but might indicate that very fragile patient condition (with several comorbidities such as diabetes mellitus and arterial disease) may be aggravated when hemodynamic instability is present and RRT is started early.

These studies were not designed to assess the effect of RRT modality (continuous or intermittent) on outcome. Thus, any attempt at drawing definite conclusions on this point would be flawed precisely for the same reasons as explained in the next section. However, intermittent hemodialysis was not associated with excess mortality compared with continuous modality in both studies, in accordance with the findings of a large RCT aimed at assessing this issue (13).

The results of both the AKIKI and IDEAL-ICU trials confirm that the indication of RRT should be based not on the *severity* of AKI (i.e., KDIGO stage) but on AKI *complications*. Whether these studies will rapidly change clinicians' practice is difficult to predict. One must keep in mind that a rather long period preceded the implementation by most clinicians of evidence-based lung-protective strategies during ventilation of patients with ARDS (65). Changes may be even slower for RRT indication during AKI, owing to strong personal beliefs and multiple sources of bias (including financial incentives in the clinical or research field) (66).

What Should *Not* Be Done When Interpreting Results of Recent RCTs

A major flaw of observational studies of severe AKI is that they included only those patients who did receive RRT. Those with AKI of similar severity who did not receive RRT were not included while having an excellent prognosis (28). The only way to avoid this flaw is to perform an RCT comparing *strategies* of RRT initiation (21). In the early RRT strategy, all patients receive RRT after randomization, but in the delayed strategy, only those patients who reach prespecified criteria (i.e., potentially severe conditions) receive RRT, thus allowing some to recover spontaneously

without RRT. It would therefore be a major methodological flaw to succumb to the temptation of comparing outcomes of patients who actually received RRT. Such analysis would only reproduce the very same pitfall of observational studies (21). The analysis of raw data from AKIKI illustrates this issue (*see* supplementary appendix of the original publication of AKIKI [7]).

Analyses, including *post hoc* ones, must be performed on baseline variables and not after artificial separation of groups according to results (67). Comparison of outcomes in patients who received early RRT with those who received late RRT is based not on baseline characteristics but solely on results and is not interpretable because of two classical major biases (which are explained in detail in a recent review published in this *Journal* [68]):

1. Indication bias (69): Patients who finally received RRT in the "delayed group" were those who needed it because of the unfavorable evolution of their health status. This results in "time-varying confounding."
2. Immortal time bias (70): Patients who received RRT in the "delayed strategy" received it not per randomized allocation but as a result of follow-up.

The problem of indication bias can be illustrated by two simple examples:

1. *Case 1*: A patient with dilated cardiomyopathy is admitted with pneumonia and impending shock and develops AKI KDIGO 3. After rapid stabilization of cardiorespiratory status, he is randomized to a "delayed RRT strategy." Two days later, his diuresis resumes, but mesenteric arterial embolization occurs during paroxysmal atrial fibrillation. Mesenteric infarction and severe shock require an operation that lasts for hours. Anuria and hyperkalemia mandate RRT (late initiation). Prognosis is very poor, but mesenteric infarction is not due to delayed RRT.
2. *Case 2*: A patient admitted for drug overdose with mild rhabdomyolysis (prolonged immobilization) and hypotension has AKI KDIGO 3. The day after allocation to early RRT (started at a time patient has recovered a perfect hemodynamic condition), the patient is conscious and extubated. AKI rapidly resolves, so RRT can be stopped after only one session. The patient is alive after 60 days. This is obviously not the consequence of early RRT.

To give a further idea of the consequences of a flawed interpretation, one can analyze the recent RCT on extracorporeal membrane oxygenation (ECMO) (71) in patients with severe ARDS. A crossover from conventional ventilation to ECMO was allowed for "rescue" in a nonnegligible number of patients who eventually had very high mortality. Artificially including these patients in the ECMO group after randomization would lead to the inescapable but completely false conclusion that ECMO is associated with a dismal prognosis.

Conclusions

The bulk of evidence indicates that "a 'wait and see' attitude can lead to avoidance of unnecessary dialysis in a large number of critically ill AKI patients without excess mortality, benefiting not only patients' outcome but also reducing costs and logistical challenges" (62) and that "a too precocious start of RRT is not helpful and might contribute further damage to an already injured kidney" (53). This watchful waiting might also enhance renal function recovery (7). Interestingly, even if a critically ill patient ultimately needs RRT, allowing some delay (if none of the aforementioned severe conditions is present) may allow initiating it in better conditions. Haste may make waste (72), and a conservative RRT strategy is in line with the tendency of doing less to gain more for ICU patients (73). In the AKIKI trial, the difference in the total number of RRT sessions between the early and delayed strategies was more than 700 (*see* supplemental material of AKIKI trial [7]).

A major international RCT (STARRT-AKI [Standard vs. Accelerated Initiation of RRT in Acute Kidney Injury]; www.clinicaltrials.gov identifier NCT02568722 [74]) led by Canadian investigators with a study design close to that of AKIKI and IDEAL-ICU is ongoing and plans to include more than 2,800 patients to detect a 6% difference in mortality in favor of an early strategy. In the same vein as AKIKI and IDEAL-ICU, the criteria that mandate RRT in the delayed strategy are rather arbitrary but should allow an adequate contrast between strategies as was true in both AKIKI and IDEAL-ICU. Its results will not be available in the near future. The implementation of this very large study was preceded by a pilot in 100 patients. No 90-day mortality difference was observed between strategies: 38% vs. 37% for the early and delayed groups, respectively ($P = 0.92$). Because AKIKI and IDEAL-ICU plus this preliminary study included more than 1,100 patients, one may reasonably consider that delaying RRT (in absence of a life-threatening situation) should become standard of care, at least tentatively pending results of the ongoing STARRT-AKI study (74).

In the majority of cases in AKIKI and IDEAL-ICU, RRT was started because of the duration of oliguria/anuria and/or because of reaching of a prespecified value of BUN. None of these conditions has proven dangerous (except for very high degrees of uremia when complicated by neurological symptoms). It is thus both scientifically and ethically sound to evaluate whether further delaying RRT, in the absence of a life-threatening complication, may allow further avoidance of unnecessary RRT. To answer this question, the AKIKI2 study (Artificial Kidney Initiation in Kidney Injury 2, funded by the French Ministry of Health; www.clinicaltrials.gov identifier NCT03396757) was recently launched and compares a "standard" strategy that corresponds to the delayed strategy in AKIKI with a "further delayed" one (in the absence of any life-threatening condition that mandates RRT). The goal is clearly not to remove RRT from the ICU armamentarium but to test the hypothesis that watchful waiting makes sense even for longer periods.

An additional argument favoring such a watchful waiting strategy is provided by the recent demonstration that sodium bicarbonate infusion in critically ill patients with severe metabolic acidemia resulted in significant reductions of the need for RRT and of mortality during severe AKI (75). Although not designed to answer the specific question of RRT timing, this study adds credence to the fact that RRT can be delayed and reserved for situations in which conservative treatment fails. By analogy, one may speculate that patients whose hyperkalemia rapidly resolves with medical treatment do

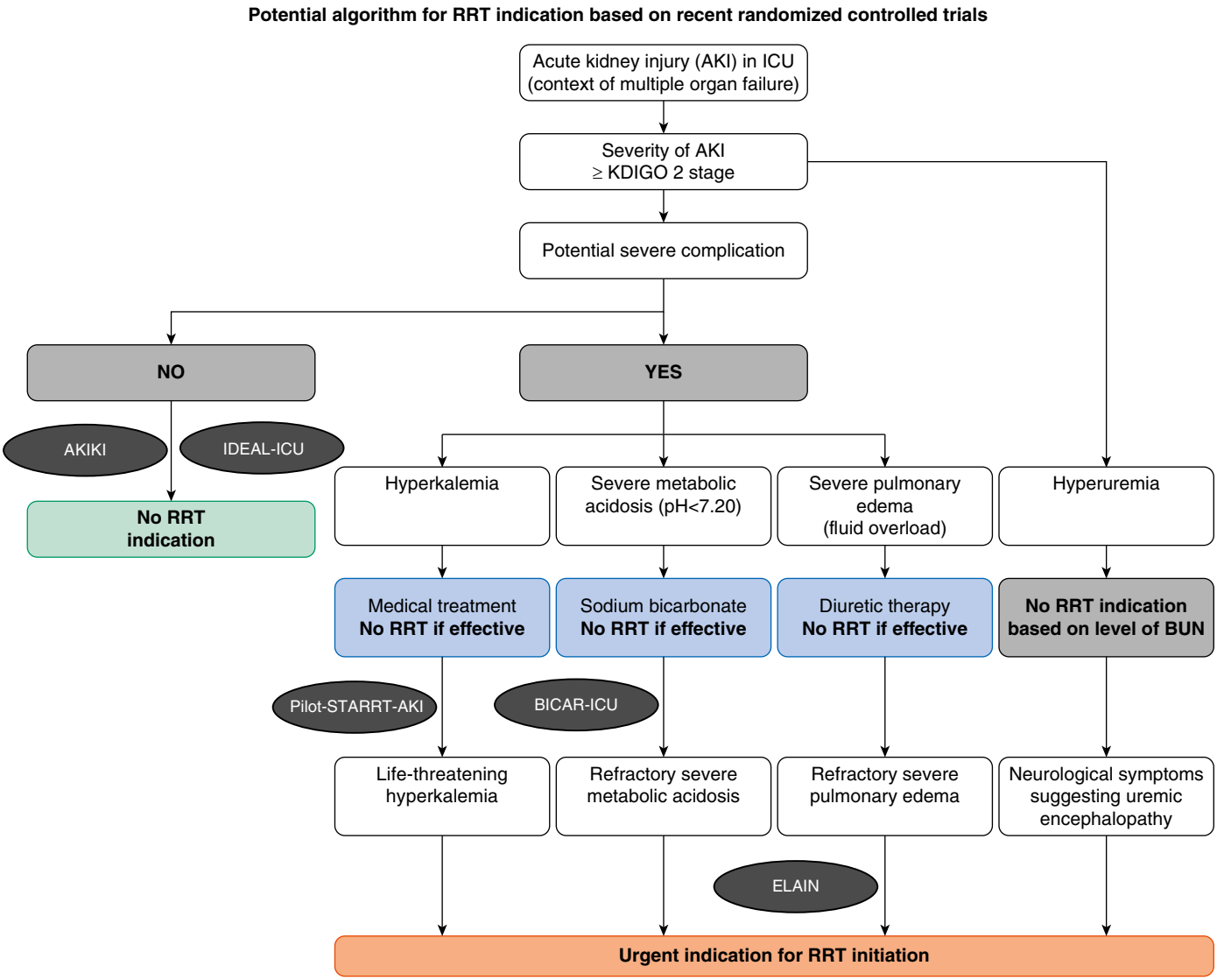

Figure 2. Potential algorithm for renal replacement therapy (RRT) indication based on recent randomized controlled trials. AKIKI = Artificial Kidney Initiation in Kidney Injury; BICAR-ICU = Sodium bicarbonate Therapy for Patients with Severe Metabolic Acidaemia in the Intensive Care Unit; BUN = blood urea nitrogen; ELAIN = Early versus Late Initiation of Renal Replacement Therapy in Critically Ill Patients with Acute Kidney Injury; IDEAL-ICU = Initiation of Dialysis Early versus Delayed in Intensive Care Unit; KDIGO = Kidney Disease: Improving Global Outcomes; STARRT-AKI = Standard vs. Accelerated Initiation of RRT in Acute Kidney Injury.

not necessarily need RRT (74). The same holds true for pulmonary edema when the use of diuretics results in an abundant diuresis. On the contrary, the ELAIN study (57) clearly confirmed that severe pulmonary edema (unresponsive to diuretics) is a mandatory indication for emergent RRT (62). Figure 2 is an attempt at summarizing the indications for RRT during AKI as they can be deduced from recent RCTs.

Taken together, the results of published studies (especially if confirmed by STARRT-AKI [74] and AKIKI2) may induce a paradigm shift in favor of a strategy of "permissive hyperuremia" by analogy to the concept of "permissive hypercapnia" that revolutionized care for patients with ARDS. If the impairment of renal recovery by an RRT strategy that is too enthusiastic ("second hit" [53]) (7, 8) is confirmed, then another concept might also emerge by analogy to the ventilator-induced injury concept that proved seminal for both experimental and clinical research on ARDS (76). This would be a time to study "artificial kidney-induced kidney injury." ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors thank patients and their surrogates who participated in the AKIKI and IDEAL-ICU trials. The authors also thank all medical and nurse teams at all study sites of AKIKI and IDEAL-ICU. In addition, the authors thank Dr. Abderrahmane Bourredjem for his help in statistical analyses.

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