Comparison of two delayed strategies for renal replacement therapy initiation for severe acute kidney injury (AKIKI 2): a multicentre, open-label, randomised, controlled trial

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Summary

Background Delaying renal replacement therapy (RRT) for some time in critically ill patients with severe acute kidney injury and no severe complication is safe and allows optimisation of the use of medical devices. Major uncertainty remains concerning the duration for which RRT can be postponed without risk. Our aim was to test the hypothesis that a more-delayed initiation strategy would result in more RRT-free days, compared with a delayed strategy.

Methods This was an unmasked, multicentre, prospective, open-label, randomised, controlled trial done in 39 intensive care units in France. We monitored critically ill patients with severe acute kidney injury (defined as Kidney Disease: Improving Global Outcomes stage 3) until they had oliguria for more than 72 h or a blood urea nitrogen concentration higher than 112 mg/dL. Patients were then randomly assigned (1:1) to either a strategy (delayed strategy) in which RRT was started just after randomisation or to a more-delayed strategy. With the more-delayed strategy, RRT initiation was postponed until mandatory indication (noticeable hyperkalaemia or metabolic acidosis or pulmonary oedema) or until blood urea nitrogen concentration reached 140 mg/dL. The primary outcome was the number of days alive and free of RRT between randomisation and day 28 and was done in the intention-to-treat population. The study is registered with ClinicalTrial.gov, NCT03396757 and is completed.

Findings Between May 7, 2018, and Oct 11, 2019, of 5336 patients assessed, 278 patients underwent randomisation; 137 were assigned to the delayed strategy and 141 to the more-delayed strategy. The number of complications potentially related to acute kidney injury or to RRT were similar between groups. The median number of RRT-free days was 12 days (IQR 0–25) in the delayed strategy and 10 days (IQR 0–24) in the more-delayed strategy (p=0·93). In a multivariable analysis, the hazard ratio for death at 60 days was 1·65 (95% CI 1·09–2·50, p=0·018) with the more-delayed versus the delayed strategy. The number of complications potentially related to acute kidney injury or renal replacement therapy did not differ between groups.

Interpretation In severe acute kidney injury patients with oliguria for more than 72 h or blood urea nitrogen concentration higher than 112 mg/dL and no severe complication that would mandate immediate RRT, longer postponing of RRT initiation did not confer additional benefit and was associated with potential harm.

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Introduction

Severe acute kidney injury is frequent among critically ill patients hospitalised in intensive care units (ICUs) and is associated with high morbidity and mortality.[1] Major uncertainty remains concerning the duration for which renal replacement therapy (RRT) can be postponed without risk as criteria for initiating RRT lack precision in the absence of complication. The majority of well conducted, randomised, controlled trials[2,3] including a recently issued very large one[4] as well as a large individual patient data meta-analysis[5] showed that an early RRT initiation strategy did not confer any survival advantage compared with a delayed strategy during severe acute kidney injury in critically ill patients when no severe complication is present.[6] Moreover, early institution of this technique was associated with more complications, some being very severe.[2,4]

The duration for which RRT initiation was delayed varied considerably, expanding from 25 hours to 57 h according to study.[2–4] The large variation in the criteria retained for initiating RRT in the delayed group of these studies[2–4] was responsible for this marked heterogeneity. The longer RRT is safely postponed, the more numerous are patients who do not receive this treatment. Severe

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Research in context

Evidence before this study

In May, 2020, we published a systematic review and individual patient data meta-analysis (IPDMA) of randomised controlled trials (RCTs), published from April, 2008, to Dec, 2019, which compared a delayed versus early renal replacement therapy (RRT) initiation strategy for severe acute kidney injury. We completed the electronic search via PubMed up until July 16, 2020, by means of the same keywords. This systematic review included ten RCTs. The complementary search found one more recent RCT (STARRT-AKI trial). The IPDMA showed that RRT initiation strategy (delayed versus early) did not affect survival in critically ill patients with severe acute kidney injury who had no urgent indications and that delayed strategies were associated with less frequent usage of RRT. The STARRT-AKI trial, a large multicentre international RCT, confirmed these findings.

The timing of early RRT initiation was roughly the same in nearly all RCTs. On the contrary, there was wide heterogeneity in the definition of delayed RRT that encompassed a delay extending from 25 to 57 h according to study. The longer the duration of delay of therapy initiation, the greater the percentage of patients who did not receive RRT. In the AKIKI trial, indications to initiate RRT in the delayed strategy were the conventional urgent indications (life-threatening metabolic complications) or oliguria for more than 72 h or a blood urea nitrogen concentration higher than 112 mg/dL. Compared with the other RCTs, this delayed strategy was associated with longer median delay (57 h) and a lower percentage of RRT initiation (51% of patients assigned to the delayed strategy).

Added value of this study

To do the present randomised trial, we considered the delayed strategy of the AKIKI trial as the standard strategy and we assessed the potential benefits of a more-delayed strategy for RRT initiation. With this new strategy the duration of oliguria was no longer an indication for RRT and the concentration of blood urea nitrogen that mandated initiation was set to higher values (140 mg/dL). The more-delayed strategy, although resulting in fewer patients receiving RRT, was not associated however with more RRT-free days which was the primary goal. Survival did not differ between groups but a prespecified multivariable analysis revealed that 60-day mortality was higher with the more-delayed strategy.

Implications of all the available evidence

This trial informs on the limit to which RRT can be safely postponed in critically ill patients with severe acute kidney injury. The more-delayed strategy was actually not associated with benefit regarding RRT-free days and was associated with higher 60-day mortality. These findings give crucial information for future guidelines which must allow maximisation of general profit by not wasting treatments and by restricting their use to the situations that really require it.

In patients with acute kidney injury stage 3 with oliguria for more than 72 h or blood urea nitrogen concentration higher than 112 mg/dL and no severe complication that would mandate immediate RRT, a longer postponing of RRT initiation does not confer additional benefit and is associated with potential harm.

hyperkalaemia or metabolic acidosis and pulmonary oedema unresponsive to diuretic administration are recognised criteria for RRT initiation.[7,8] In the absence of such complications, the extent to which the duration of oliguria or anuria, or the degree of uremia constitute an appropriate indication for RRT is unknown. Establishing evidence-based criteria for both pertinent and safe initiation of RRT might help rationalise the use of this costly treatment.

The AKIKI 2 (Artificial Kidney Initiation for Kidney Injury 2) trial was a non-blinded multicentre, randomised, controlled trial that compared two delayed strategies for RRT initiation. One was exactly the same as the one used in our previous study.[2] In this previous study, the delayed strategy proved safe and resulted in the longest reported delay between the onset of severe acute kidney injury and RRT initiation in randomised, controlled trials.[2–4,9] The second strategy tested in the present study was more delayed as it allowed further postponing of RRT initiation in the absence of the abovementioned complications. The aim of the study was to test the hypothesis that this more-delayed initiation strategy would result in more RRT-free days, a composite outcome of duration of RRT and survival[10] compared with the delayed strategy.

Methods

Study design

The AKIKI 2 study was an institutionally sponsored unmasked, multicentre, open-label, two-arm, randomised, controlled trial done in 39 intensive care units in France. A complete list of participating sites is provided in the appendix (pp 2–4). The study protocol (previously published[11]) was approved by the competent French legal authority (Comité de Protection des Personnes de Sud-Est V) for all participating centres. All analyses were done in accordance with the International Conference on Harmonization and Good Clinical Practice guidelines.

Participants

Eligible patients were adults (18 years of age or older) hospitalised in the ICU with acute kidney injury who were receiving (or had received for this episode) invasive mechanical ventilation or catecholamine infusion, or both. Patients with stage 3 acute kidney injury (Kidney Disease: Improving Global Outcomes [KDIGO] classification)[8] were monitored for occurrence of one of the following criteria: oliguria or anuria (urine output <0·3 mL/kg per h or <500 mL/day) for more than 72 h (3 consecutive days) or blood urea nitrogen concentration between 112 mg/dL

(serum urea concentration of 40 mmol/L) and 140 mg/dL (serum urea concentration of 50 mmol/L). Such criteria were exactly the same as those mandating the initiation of RRT in the delayed group in our previous study.[2] Patients reaching one of these criteria were allocated to one of the two groups of this study: delayed (in which RRT was started just after randomisation) or more-delayed (in which RRT initiation was postponed). Patients presenting with an urgent indication for RRT (appendix p 11) before reaching criteria for randomisation received immediate treatment and were not included. Other non-inclusion criteria are detailed in the appendix (p 7).

All patients (or their surrogates) who were monitored for occurrence of randomisation criteria were informed about the study both verbally and with a written document in accordance with French law. At the time of randomisation, written informed consent was obtained from patients or surrogates, or through a process of deferred consent.

Randomisation and masking

The randomisation list was computer-generated, balanced by blocks of variable and undisclosed size, and stratified per centre. Patients were randomly assigned in a 1:1 ratio to a delayed or more-delayed RRT strategy. Allocation concealment was achieved by means of a centralised, secure, interactive, web-response system accessible from each study centre (Cleanweb, Telemedecine Technologies SAS, Boulogne-Billancourt, France).

Procedures

Patients allocated to the delayed strategy (ie, the same strategy as in our previous study[2]) were to have RRT initiated within 12 h after fulfilling the randomisation criteria.

In the more-delayed strategy, RRT was postponed until one urgent indication occurred (appendix p 11) or if blood urea nitrogen concentration reached 140 mg/dL (serum urea concentration of 50 mmol/L) for one day. The duration of anuria was not a criterion for initiation. The decision to initiate RRT had to be approved by the attending physician(s) involved in the patient's care.

Management of RRT (including choice of intermittent or continuous technique, duration and interval between sessions, device setting, or anticoagulation modality) was left to the discretion of each study site and was prescribed and monitored according to national guidelines.[12] Prevention of dialysis disequilibrium syndrome was recommended when initial blood urea nitrogen was high (>112 mg/dL).[11] Several measures were suggested: slow gentle initial haemodialysis, increasing dialysate sodium concentrations, use of a high-glucose-concentration dialysate, or administering hypertonic glucose in the venous line of the dialyser during dialysis. In both groups, RRT discontinuation was contemplated if spontaneous diuresis was 500 mL/24 h or more, and highly recommended if diuresis was more than 1000 mL/24 h spontaneously or more than 2000 mL/24 h in patients receiving diuretics. Discontinuation was mandatory when diuresis was sufficient to allow for spontaneous serum creatinine concentration decrease. If improvement of renal function was insufficient to achieve a spontaneous decrease in creatinine concentration or if diuresis became lower than 1000 mL/24 h without diuretics (or lower than 2000 mL/24 h under diuretics), or both, RRT was resumed. The duration of follow-up for each patient was 60 days.

Outcomes

The primary outcome was the number of RRT-free days between randomisation and day 28. For each patient, one point was given for each calendar day that a patient was both alive and free of RRT, assuming that the patient survived and remained free of the technique for at least 3 consecutive calendar days after RRT weaning, whatever the vital status at day 28. Zero RRT-free day value was assigned to patients who died before weaning or who remained dependent on RRT until day 28.

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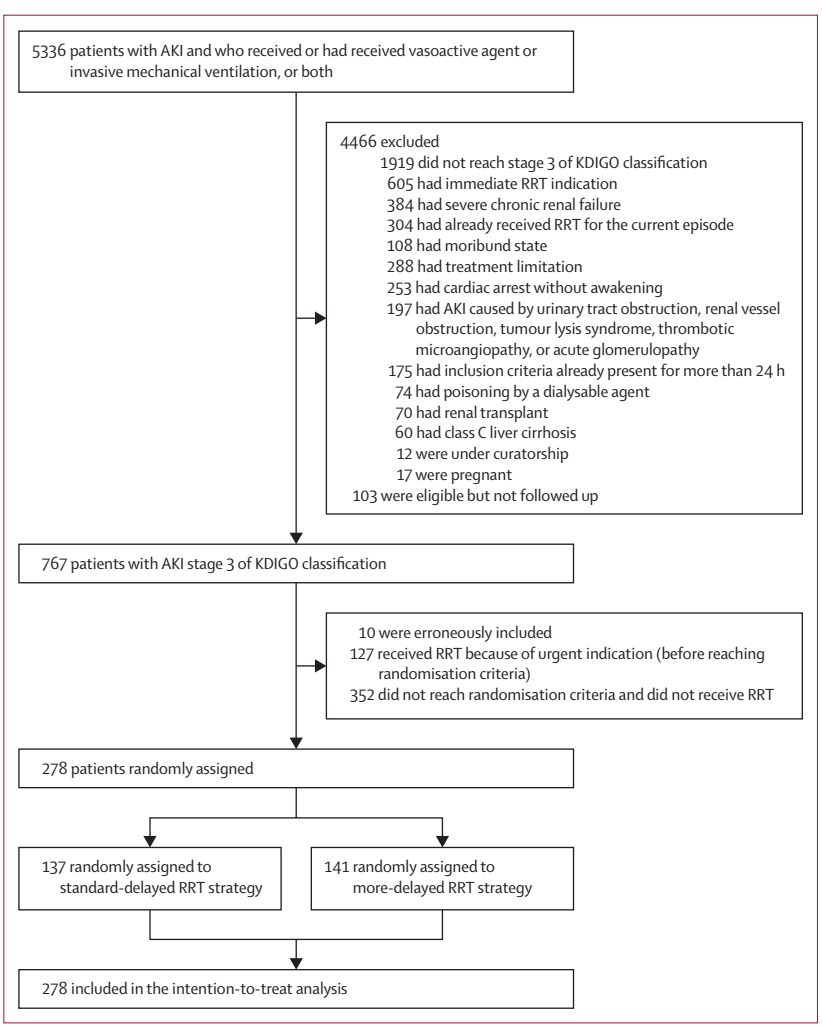

***Figure*: Trial profile**
AKI=acute kidney injury. KDIGO=Kidney Disease: Improving Global Outcomes. RRT=renal replacement therapy.

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Secondary outcomes were the vital status at ICU and hospital discharge, at day 28 and 60, the percentage of patients receiving RRT at least once, the number of RRT sessions between randomisation and day 28, the time between inclusion in the observational stage and RRT initiation, the number of patients with renal function recovery (as defined in the appendix p 5) between randomisation and day 60, the number of ventilator-free and catecholamines-free days between randomisation and day 28, the duration from randomisation and both ICU and hospital discharge, the reason for initiation of RRT, its modalities and duration, the number of dialysis catheter-free days between randomisation and day 28, the rate of catheter-related (both dialysis and non-dialysis catheters) bloodstream infection, the Barthel Activities of Daily Living Index at day 60,[13] the complications potentially related to acute kidney injury or RRT (appendix pp 5–6), the number of patients with treatment limitation, hydration (weight, clinical oedema scale, and fluid balance), and nutritional status (modified Nutrition Risk in Critically ill score,[14] serum albumin, transthyretin, and C-reactive protein concentration). We initially planned to report the amount of calories and of protein administered but the number of missing data precluded any proper analysis. A medico-economic analysis will be reported in another manuscript.

We did a post-hoc analysis in order to analyse the primary outcome and mortality at day 60 as a function of the criterion that mandated randomisation (oliguria or anuria for more than 72 h or blood urea nitrogen concentration of 112 mg/dL [serum urea concentration of 40 mmol/L]).

	At onset of monitoring (KDIGO stage 3)	Upon randomisation	
	n=757	Delayed RRT group (n=137)	More-delayed RRT strategy group (n=141)
Age	65 (13)	65 (13)	65 (12)
Sex			
Female	235 (31%)	35 (26%)	38 (27%)
Male	522 (69%)	102 (74%)	103 (73%)
Serum creatinine before intensive care unit admission, mg/dL*	0·98 (0·33)	1·08 (0·36)	1·08 (0·41)
Coexisting condition			
Chronic renal failure	76 (10%)	17 (12%)	16 (11%)
Hypertension	424 (56%)	81 (59%)	84 (60%)
Diabetes	192 (25%)	40 (29%)	31 (22%)
Congestive heart failure	47 (6%)	9 (7%)	6 (4%)
Ischaemic heart disease	79 (10%)	15 (11%)	21 (15%)
Simplified Acute Physiology Score III	70 (15)	73 (14)	72 (13)
Sepsis-related Organ Failure Assessment	11 (3)	12 (3)	11 (4)
Physiological support			
Invasive mechanical ventilation	574 (76%)	113 (82%)	115 (82%)
Vasopressor support (epinephrine or norepinephrine)	601 (79%)	94 (69%)	80 (57%)
Exposure to at least one nephrotoxic agent in past 2 days	367 (48%)	63 (46%)	65 (46%)
Septic shock	405 (54%)	81 (59%)	79 (56%)
Acute respiratory distress syndrome	226 (30%)	53 (39%)	51 (36%)
Biological characteristics†			
Serum creatinine, mg/dL	2·6 (1·8)	5·0 (2·0)	5·9 (2·2)
Blood urea nitrogen, mg/dL	47 (31)	92 (29)	107 (28)
Serum potassium, mmol/L	4·4 (0·9)	4·4 (0·8)	4·6 (0·8)
Serum bicarbonate, mmol/L	19·5 (6·0)	19·4 (4·2)	18·4 (5·2)

Data are mean (SD) or n (%). To convert values for creatinine to micromoles per litre, multiply by 88·4. To convert values for blood urea nitrogen to millimoles per litre, multiply by 0·357. KDIGO=Kidney Disease Improving Global Outcome. RRT=renal replacement therapy. *Serum creatinine concentration before intensive care unit admission was determined by the results of a measurement in the 12 months preceding the intensive care unit stay or estimated. †Biological characteristics are provided at the time of onset of monitoring of patients with stage 3 acute kidney injury and at the time of randomisation.

Table 1: **Baseline characteristics**

Statistical analysis

On the basis of the AKIKI trial,[2] mean number of RRT-free days at day 28 in the delayed strategy was expected to be 17 days. We assumed that the more-delayed strategy would increase this parameter to 21 days (an increase of 4 days—ie, approximately 25%). Considering a drop-out rate of approximately 5%, total sample size required was 270 (135 in each group) to detect this difference with 80% power (α=5%, bilateral formulation). We planned to stop enrolment at the screening stage after the randomisation of 270 patients.

An interim analysis of survival and complication rate at day 28 was done blinded by an independent Data Safety Monitoring Board after the follow-up completion of the first 135 patients. No specific analysis strategy was necessary to maintain an overall type I error rate because the primary outcome was not assessed at the interim analysis.

We checked the normality of the distribution of the primary endpoint by means of a Shapiro-Wilk test. RRT-free days were described by means of median (IQR; 25th percentile to 75th percentile) and compared between the two groups by means of a non-parametric Wilcoxon rank-sum test.

Categorical endpoints were compared by means of the χ-squared or Fisher's exact test, as appropriate. Continuous endpoints were compared by means of the Student's *t* or Wilcoxon test, as appropriate.

To assess the prognostic factors potentially involved in 60-day mortality and to improve the estimation accuracy of the RRT initiation strategy effect on 60-day mortality, we did a prespecified analysis[11] with a multivariable Cox regression model. The fixed effects measured at baseline were the same as in our previous study[2]: randomisation group, Simplified Acute Physiology Score III,[15] catecholamine infusion (epinephrine or norepinephrine), invasive mechanical ventilation, sepsis, and time between admission to ICU and acute kidney injury development.[2] The centre was introduced as a random

effect. Hazard ratio (95% CI) was reported for each prognostic factor. All analyses were done at the bilateral α risk of 5%, by means of R software (version 3.5.1). The study was overseen by a steering committee (SG, DH, J-PQ, DD). The trial was registered at ClinicalTrials.gov, NCT03396757; date of registration, Jan 11, 2018.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between May 7, 2018, and Oct 11, 2019, of 5336 patients assessed, 767 patients with KDIGIO stage 3 acute kidney injury were monitored for occurrence of randomisation criteria. Ten were excluded for erroneous inclusion. Among 757 remaining patients, 278 (37%) underwent random assignment (figure). The characteristics and outcomes of the 479 patients who were not randomly assigned are presented in the appendix (p 12). Patient characteristics at the time of KDIGO stage 3 acute kidney injury and on random assignment are reported in table 1. The concentration of both serum creatinine and blood urea nitrogen was markedly higher at the time of randomisation than at the time of KDIGO stage 3 acute kidney injury occurrence when patient monitoring for randomisation criteria was started.

Among 757 eligible patients with KDIGO stage 3 acute kidney injury, 127 patients received RRT without being randomly assigned because of urgent indication (figure). The median time between KDIGO stage 3 acute kidney injury occurrence and RRT initiation was 35 h (IQR 17–68) in these 127 patients.

Of the 278 patients who underwent random assignment, 137 were assigned to the delayed strategy and 141 to the more-delayed strategy. The distribution of criteria (oliguria or anuria of more than 72 h or blood urea nitrogen concentration >112 mg/dL) that triggered inclusion is provided in the appendix (p 14). With the delayed strategy, 134 (98%) received RRT within a median time of 44 h (IQR 23–66) from eligibility (3 h [IQR 2–5] from randomisation and 96 h [72–120] from ICU admission). With the more-delayed strategy, 111 (79%) patients received RRT within a median time of 94 h (IQR 59–130) from eligibility (33 h [IQR 24–60] from randomisation and 168 h [96–216] from ICU admission). Biological characteristics at the time of RRT initiation are described in the appendix (p 15). Distribution of criteria that mandated RRT initiation in the more-delayed strategy group is described in the appendix (p 16). Intermittent haemodialysis was more frequently used than continuous technique as first RRT session in both randomisation groups. Details on modalities are provided in the appendix (p 17). In the first 7 days following randomisation, 137 (49%) of 278 patients received diuretics (69 [50%] of 137 in the delayed strategy and 68 [48%] of 141 in the more-delayed strategy).

For the primary outcome, in the intention-to-treat analysis, the number of RRT-free days did not differ between the delayed strategy (12 days [IQR 0–25]) and the more-delayed strategy (10 days [IQR 0–24]; p=0·93; table 2).

60-day mortality did not differ significantly between groups. 60 (44%) of 137 patients in the delayed strategy group died and 77 (55%) of 141 in the more-delayed

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See Online for appendix

	Delayed RRT strategy group (n=137)	More-delayed RRT strategy group (n=141)	p value
RRT-free days			
All patients	12 (0–25)	10 (0–24)	0·93
Survivors	24 (15–27)	23 (14–28)	0·54
Number of patients who actually received RRT	134 (98%)	111 (79%)	<0·0001
Time from randomisation to RRT, h	3 (2–5)	33 (24–60)	<0·0001
Number of RRT sessions*	5 (2–10)	5 (2–10)	0·75
Duration of RRT days*	5 (2–10)	5 (2–10)	0·75
Modality, first day*			
Intermittent RRT	81 (60%)	64 (58%)	0·53
Continuous RRT	52 (39%)	44 (40%)	..
Both modalities	1 (1%)	3 (3%)	..
Mortality			
At day 28	52 (38%)	63 (45%)	0·26
At day 60	60 (44%)	77 (55%)	0·071
At ICU discharge	55 (40%)	66 (47%)	0·26
At hospital discharge	61 (45%)	75 (53%)	0·15
Patients with treatment limitation in the ICU	37 (27%)	45 (32%)	0·39
Ventilator-free days	0 (0–17)	0 (0–19)	0·59
Vasopressor-free days	21 (3–27)	15 (0–27)	0·28
Length of ICU stay	18 (12–31)	16 (10–32)	0·64
Length of hospital stay	34 (17–51)	29 (15–58)	0·74
Renal function recovery at day 60†	21 (51)	29 (69)	0·10
RRT dependence‡			
At day 28	13 (16)	7 (11)	0·33
At day 60	3 (4)	1 (2)	0·62
Hydration status			
Weight at day 7, kg	92 (19)	90 (21)	0·15
Clinical oedema scale at day 7§	..	..	0·85
Absence	34 (38%)	32 (41%)	..
Mild	19 (21%)	17 (22%)	..
Moderate	21 (23%)	19 (24%)	..
Severe	16 (18%)	10 (13%)	..
Cumulative fluid balance, mL			
After 2 days	1584 (3406)	1581 (2800)	0·99
After 7 days	1744 (8338)	2072 (8158)	0·79
Nutritional status at day 7			
Simplified NUTRIC score	5 (3–6)	5 (3–6)	0·92
Serum albumin, g/L	18 (41)	26 (49)	0·91
Serum transthyretin, mg/L	21 (54)	30 (75)	0·95
Serum C-reactive protein, mg/L	27 (65)	32 (71)	0·41
Catheter-related bloodstream infection	18 (13%)	15 (11%)	0·52
Number of dialysis catheter-free days	6 (0–20)	3 (0–19)	0·75

(Table 2 continues on next page)

	Delayed RRT strategy group (n=137)	More-delayed RRT strategy group (n=141)	p value
(Continued from previous page)			
Complications potentially related to AKI or RRT¶			
Haemorrhage	24 (18%)	30 (21%)	0·43
Thombocytopenia	63 (46%)	64 (45%)	0·95
Thrombosis	7 (5%)	2 (1%)	0·10
Hypokalaemia	27 (20%)	34 (24%)	0·37
Hyperkalaemia	12 (9%)	8 (6%)	0·32
Hyponatraemia	12 (9%)	18 (13%)	0·28
Hypernatraemia	24 (18%)	17 (12%)	0·20
Hypophosphataemia	18 (13%)	21 (15%)	0·66
Cardiac rhythm disorders			
Severe	4 (3%)	4 (3%)	1·00
Moderate	26 (19%)	20 (14%)	0·26
Pneumothorax	4 (3%)	3 (2%)	0·72
Haemothorax	0	0	1·00
Air embolism	0	0	1·00
Arteriovenous fistula	0	0	1·00
Pericarditis	0	0	1·00
Unexpected cardiac arrest	8 (6%)	7 (5%)	0·73
Hypothermia	4 (3%)	4 (3%)	1·00
Barthel Activities of Daily Living Index	13 (10–24)	12 (10–18)	0·22

Data are median (IQR), mean (SD), or n (%). Details regarding the modified NUTRIC score and the oedema scale are provided in the appendix (pp 9–10). RRT=renal replacement therapy. ICU=intensive care unit. NUTRIC score=Nutrition Risk in Critically ill score.[14] AKI=acute kidney injury. *For patients who received at least one RRT session (n=134). †Renal function recovery is reported for patients who survived and for whom serum creatinine concentration determination was available at day 60. ‡RRT dependence is reported for patients who survived at day 28 and day 60. §For patients for whom we have the data (n=90). ¶Definitions of complications potentially related to AKI or RRT are provided in the appendix (pp 5–6).

Table 2: **Primary and secondary outcomes**

	Univariable analysis		Multivariable analysis	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
More-delayed strategy	1·34 (0·96–1·89)	0·13	1·65 (1·09–2·50)	0·018
Simplified Acute Physiology Score III	1·03 (1·02–1·05)	<0·0001	1·03 (1·01–1·05)	0·0005
Mechanical ventilation	2·90 (1·47–5·70)	<0·0001	3·44 (1·52–7·81)	0·0020
Catecholamine infusion	1·69 (1·17–2·44)	0·0080	1·13 (0·69–1·84)	0·64
Sepsis status	..	0·064	..	0·19
Sepsis	0·78 (0·47–1·30)	..	0·56 (0·28–1·12)	..
Septic shock	1·44 (0·98–2·12)	..	0·91 (0·51–1·64)	..
Time between ICU admission and acute kidney injury	0·69 (0·36–1·31)	0·24	0·70 (0·31–1·59)	0·39

ICU=intensive care unit.

Table 3: **Multivariable analysis of risk factors for day-60 mortality**

strategy died (p=0·071). However, in a multivariable analysis, risk factors associated with 60-day mortality were more-delayed strategy (HR 1·65; 95% CI 1·09–2·50, p=0·018), Simplified Acute Physiology Score III (HR 1·03; 95% CI 1·01–1·05, p=0·0005), and mechanical ventilation (HR 3·44; 95% CI 1·52–7·81, p=0·0020; table 3). Other secondary outcomes including RRT dependence at day 60 and complications potentially related to acute kidney injury or RRT did not differ between groups (table 2). The 2-day and 7-day cumulative fluid balance did not differ between delayed RRT and more-delayed RRT (1584 [3406] mL *vs* 1581 [2800] mL and 1744 [8338] mL *vs* 2072 [8158] mL). The same was true for other indicators of hydration (weight and oedema scale) as well as for nutritional status (table 2). Serum creatinine values at different stages are presented in the appendix (p 18).

RRT-free days and day-60 mortality did not differ between strategies when patients were analysed according to the criteria that mandated randomisation (oliguria or anuria for more than 72 h or blood urea nitrogen concentration of 112 mg/dL). This post-hoc analysis is presented in the appendix (p 19).

Discussion

This study compared two delayed strategies for RRT initiation in critically ill patients with severe acute kidney injury. The first was similar to the strategy that allowed for important and safe reduction of the number of patients receiving this treatment in our previous study.[2] The second tested the possibility to further increase this number by postponing RRT initiation for an even longer period. This was achieved by two specifications of the protocol: the duration of oliguria or anuria was no longer an indication for initiating RRT (contrarily to the AKIKI study[2]) and the concentration of blood urea nitrogen that mandated initiation was set to a higher value (140 mg/dL instead of 112 in the AKIKI study) in the more-delayed strategy. This more-delayed RRT strategy, although resulting in fewer patients receiving treatment, was not associated with more RRT-free days, which was the primary goal. Survival did not differ between groups either at day 28 or day 60. However, a multivariable analysis revealed that 60-day mortality was higher with the more-delayed strategy.

Timing of RRT initiation during acute kidney injury has been the subject of several randomised, controlled studies. A strategy of immediate RRT initiation conferred survival advantage in a single-centre randomised trial in patients with fluid overload and pulmonary oedema for a noticeable proportion.[16] Conversely, two multicentre single-country trials,[2,3] a very large international trial[4] and a large individual patient data meta-analysis[5] clearly showed that RRT should not be initiated in emergency when the only marker of severity is the KDIGO stage 3 injury (which is the highest severity in acute kidney injury classification[8]). Indeed, mortality rate did not significantly differ between early and delayed strategies, and significantly less severe adverse effects as well as better renal recovery were observed when RRT was delayed in patients who had no severe complication of acute kidney injury on inclusion.[2,4]

The results of these studies close an intense debate that has lasted for many years.[5,17] However, a last difficulty

remains in defining the appropriate duration of the postponement of RRT. This stems from the wide magnitude of difference in the delay before RRT initiation between patients allocated to an early or delayed initiation strategy. It was modest in some studies[4,9] and much larger in others.[2,3] This is no trivial matter as a longer delay results in lesser use of devices and enables a substantial number of patients to recover from acute kidney injury without undergoing RRT. Of note, the longer the duration of delay of therapy initiation, the greater the percentage of patients who did not receive RRT: median delay was 25 h in the STARRT-AKI study,[4] 48 h in the IDEAL-ICU trial[3] and 57 h in the AKIKI study[2] and patients who avoided RRT ranged from 38%[4] to 49%.[2] The longer delay was observed in the AKIKI study[2] because the protocol allowed for a prolonged duration of oliguria or anuria (72 h) or for a high blood urea nitrogen concentration (>112 mg/dL) before initiating RRT in the (then-termed) delayed strategy. However, the upper limit boundary in terms of delay to initiate RRT in the absence of severe complication remained to be established. Deleting oliguria or anuria duration as a criterion for initiating RRT and increasing the threshold of blood urea nitrogen allowed for testing the practicability and safety of an extension of the delay of initiation in the present study.

It is important to note that values for blood urea nitrogen at the onset of monitoring of patients with KDIGO stage 3 acute kidney injury in this study (table 1) were similar to those in patients allocated to the early initiation strategy in our previous study.[2] Likewise, values for blood urea nitrogen at the time of randomisation in the present study were similar to those measured at the time of RRT initiation in patients assigned to the delayed strategy in the previous study.[2] This forms the basis for the comparison of two delayed strategies.

As already mentioned, a more-delayed strategy further reduced the number of patients who ultimately received RRT but this did not translate into increased RRT-free days. This is likely to be the result of competing risk between the use of a technique and survival.[10]

Mortality was not significantly different between strategies. The mortality endpoint should be viewed as a safety endpoint complementing the primary efficacy endpoint. A p value of 0·071 in univariable analysis can be seen as a warning signal against the more delayed strategy. The prespecified analysis[11] of adjusted day-60 mortality revealed a significant increase in mortality with the more-delayed strategy. The reasons for this finding are unclear as there were no differences between strategies in the rate of complications, or in the length of ICU and hospital stay. Neither the analysis of hydration or nutritional status nor the post-hoc analysis according to renal inclusion criteria showed significant difference between strategies. We might only speculate on a potential deleterious role of accumulation of putative toxins when RRT initiation was more delayed.

Renal function recovery and RRT dependency were not differentially affected. Similarly, non-renal organ failure-free days did not differ between strategies. The observed number of RRT-free days in the more-delayed strategy was shorter compared with the data of the AKIKI 1 trial (12 *vs* 17 days). This difference might be because patients in the AKIKI 2 study were randomly assigned later in their follow-up. Nevertheless, we cannot exclude that this new study is underpowered to detect an increase of 25% of the number of RRT-free days.

Whereas the risk associated with severe hyperkalaemia and metabolic acidosis or pulmonary fluid overload that does not respond to diuretics is obvious and mandates RRT initiation, there is a lack of evidenced-based data on how the concentration of blood urea nitrogen should dictate this treatment. Whether a certain concentration of blood urea nitrogen should be a criterion mandating the initiation of RRT has been highly debated.[7,8,18] An expert group of the Acute Kidney Injury Network stated that a blood urea nitrogen concentration of more than 100 mg/dL constitutes an absolute indication for RRT[18] despite lack of objective data. Median concentration of blood urea nitrogen was 90 mg/dL at the time of RRT initiation in the delayed strategy of the AKIKI study.[2] There was no difference in mortality with the early strategy in which this concentration was much lower.[2] In the present study, the concentration of blood urea nitrogen was allowed per protocol to rise greater than 112 mg/dL in the more-delayed strategy. This strategy was associated with a worsened prognosis. This study gives objective credence to the limit that the concentration of blood urea nitrogen should not exceed.

The choice of criteria for RRT initiation warrants discussion. Any threshold for urea concentration is necessarily arbitrary as there is no obvious direct link between blood urea nitrogen concentration and mortality. We chose a value of 140 mg/dL for the more-delayed strategy because it was 25% higher than the 112 mg/dL concentration in the delayed group of this study (and was shown to be a safe criterion for RRT initiation in the delayed group of the AKIKI study). This allowed for a significant contrast between strategies. Obviously, there is necessarily some arbitrary choice when comparing two contrasted strategies. This was the case in many studies in patients in the ICU (comparison of two thresholds for blood transfusion,[19] of two tidal volume values during mechanical ventilation of patients with acute respiratory distress syndrome,[20] or two values for mean arterial pressure during treatment of septic shock[21]). Similarly, the concentration of serum potassium that mandated RRT initiation was moderately high but very similar to that in other RCTs in the same field, including the very large STARRT-AKI trial.[4] A higher concentration might have been chosen but was not devoid of potential risk in critically ill patients.

Fair allocation of limited resources is not only based on individual considerations but at least as importantly

on wise general guidelines. More frequent or intensive use of devices or treatments do not necessarily equate with better medicine and better prognosis.[22] Guidelines must allow maximisation of general profit by not wasting treatments and by restricting their use to the situations that really require them. The COVID-19 crisis leads to many critically ill patients receiving RRT[23] whereas shortage of devices is impending.[24] Knowing to what extent RRT initiation can be postponed is of paramount importance in this context among others. This study provides arguments to answer this question.

Contributors

All authors had access to all of the data. SGa, DH, LM-L, SL, JR, J-DR, J-PQ, and DD were responsible for the design, analysis, and writing of the manuscript. GLa, SM, DT-B, BLC, BP, NdP, SBe, AC, AR, MB, JBa, GC, JBo, EC , NC, SBa, CV, J-MF, DT, EB, KL, NA, SGr, ML, GLo, SN, FP, JM, KA, GG, KK, GT, LA BR, CC, and PA were responsible for recruitment and clinical care of the patients. DH and SL accessed and verified the data. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors reviewed and approved the final version of the manuscript.

Declaration of interests

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Data sharing

Anonymous participant data is available under specific conditions. Proposals will be reviewed and approved by the sponsor, scientific committee, and staff on the basis of scientific merit and absence of competing interests. Once the proposal has been approved, data can be transferred through a secure online platform after the signing of a data access agreement and a confidentiality agreement.

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