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Timing of renal replacement therapy in acute kidney injury: case closed?

Acute kidney injury is a common syndrome defined by an acute deterioration in renal function, and affects a wide variety of patients. It encompasses a heterogeneous group of underlying causes and thereby variable pathophysiological processes.[1] In high-income countries, acute kidney injury is frequently associated with multiple organ failure, as well as sepsis, use of nephrotoxic drugs, and major surgery. In low-income and middle-income countries (LMICs), however, it is more likely to be associated with a single disease.[2] Among community-dwelling patients in LMICs, acute kidney injury is often associated with environmental factors such as endemic infections or contaminated water, whereas in inpatients, the aetiology resembles that among patients in high-income countries.[2] Although the exact worldwide incidence and prevalence of acute kidney injury are uncertain because of variability in reporting systems (eg, the Risk, Injury, Failure, Loss, and End-stage renal disease criteria, the Acute Kidney Injury Network criteria, or the Kidney Disease: Improving Global Outcomes [KDIGO] criteria), absence of baseline serum creatinine concentration data, or non-availability of data (especially in LMICs), acute kidney injury is estimated to occur in 10–15% of all hospitalised patients, increasing to 50% in those admitted to intensive care units.[3–5]

Acute kidney injury is associated with increased morbidity, mortality, and costs of care, not only as a consequence of impaired renal function but also because of remote tissue injury caused by the generalised inflammatory response induced by the syndrome. Hospital mortality rates vary from 10% to 20%, and correlate strongly with the severity of renal dysfunction.[6–8] In addition, acute kidney injury is associated with development of chronic kidney disease and negatively influences long-term outcomes and survival for up to 10 years after the primary insult.[8,9] It is imperative that, where possible, acute kidney injury is prevented, the diagnosis is made swiftly and correctly, and the treatment is initiated at an early stage. If the syndrome proceeds, renal replacement therapy (RRT), in the form of continuous venovenous haemofiltration, haemodialysis, or haemofiltration, might be indicated to correct life-threatening complications such as fluid, acid–base, and electrolyte imbalances. In everyday practice, the decision to start RRT is frequently more arbitrary, as physicians consider the overall clinical context of the patient. The optimal timing of RRT initiation in the absence of these complications is therefore a subject of ongoing debate and is not known.[10,11]

In *The Lancet*, Stéphane Gaudry and colleagues[12] report the results of an individual patient data meta-analysis addressing this important topic. Data from randomised clinical trials published between 2008 and 2019 were included if they compared delayed with early initiation of RRT in critically ill patients with acute kidney injury of KDIGO stage 2 or 3. The primary outcome was


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28-day all-cause mortality. From the ten eligible studies (2143 patients), individual patient data were obtained from the investigators of nine studies, and the final analysis was done with data from 1879 (88%) patients: 946 in the delayed RRT group (609 [64%] men, 337 [36%] women; mean age 64·3 years [SD 15·9]) and 933 in the early RRT group (591 [63%] men, 342 [37%] women; 63·5 years [15·4]). Mortality at day 28 after randomisation (the primary outcome) was not significantly different between the delayed RRT group (366 [44%] of 837 patients with available data) and the early RRT group (355 [43%] of 827; risk ratio 1·01 [95% CI 0·91–1·13]), and nor was the 60-day or 90-day mortality. Gaudry and colleagues concluded that the timing of RRT did not affect survival in critically ill patients with severe acute kidney injury who had no urgent indications for RRT. No significant interactions were found between baseline characteristics (including age and sex) and treatment effect.

This well designed study involved data from almost all relevant randomised clinical trials from the past decade, including a representative group of patients with various pathophysiological mechanisms underlying acute kidney injury. The authors should be congratulated for this achievement and the worldwide collaboration that facilitated this analysis.

One limitation of the study is that, as the authors indicated, the definitions of early and delayed initiation of RRT varied among the included studies. Additionally, the studies differed in the type and dosage of RRT administered. Nevertheless, minimal heterogeneity was found across the studies, and the use of individual patient data is a particular strength here.

In the subgroup analysis, no difference in outcome was found between patients with and without pre-existing chronic kidney disease. However, more data are needed to clarify the potential differences in the effects of RRT timing between different patient subgroups. The STARRT-AKI trial of more than 3000 patients, the results of which are yet to be published, should provide sufficient power for subgroup analyses, including comparisons among patients with and without sepsis, and should also provide useful information on long-term quality of life in this population.[13]

Although Gaudry and colleagues did not find differences in complication rates between groups, it is possible that complications related to the early start of RRT might have been under-reported. These results contrast with those of a previous Cochrane meta-analysis, in which more complications were found in the early RRT group.[14] Additionally, Gaudry and colleagues reported that 42% of patients in the delayed group never received RRT, which could have the advantage of allowing scarce resources to be saved. Unfortunately, this meta-analysis showed no significant increase in RRT-free days in the delayed group compared with the early group, although the authors note that this lack of difference might have been due to a methodological issue.

Overall, this meta-analysis shows that early initiation of RRT is not associated with improved outcome, and seems to support a delayed initiation strategy in critically ill patients, on the basis that a delay might avoid the need for any RRT in these patients.

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The key role of palliative care in response to the COVID-19 tsunami of suffering

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Coronavirus disease 2019 (COVID-19) has brought a tsunami of suffering that is devastating even well resourced countries. The disease has wreaked havoc on health systems and generated immense losses for families, communities, and economies, in addition to the growing death toll. Patients, caregivers, health-care providers, and health systems can benefit from the extensive knowledge of the palliative care community and by taking heed of long-standing admonitions to improve access to essential medicines, particularly opioids for the relief of breathlessness and pain.[1–3]

For low-income and middle-income countries (LMICs), the COVID-19 pandemic is likely to be even more severe than in high-income countries. There will probably be a high burden of COVID-19 in settings where there are weak health-care systems, lack of access to clean water and disinfectants, poor outbreak preparedness, severe shortages in personal protective equipment (PPE) and medical technology, challenges in enforcing physical distancing regulations, and reliance on informal employment. In such settings, it is expected that patients with severe COVID-19 who are unable to access the limited supply of intensive care resources or hospital beds will suffer and die at home, where they would be cared for by family members without PPE and access to relevant information, training, or palliative care resources. These caregivers will probably become infected and spread the disease. Additionally, if resources are reallocated to respond to COVID-19, patients with other life-limiting conditions could find themselves pushed out of their health-care settings with reduced access to opioid medication.

During the COVID-19 pandemic, access to essential palliative care at end-of-life, including bereavement support, will be limited in the face of high demands in all countries. There will be increased isolation and suffering for palliative care patients and those who are bereaved.[4,5] Strict physical distancing regulations to slow disease transmission mean that patients who die from COVID-19 will usually be without loved ones by their side, who in turn will be unable to say goodbye or undertake traditional grieving rituals.[4,6] Providers of palliative care, including private hospices, will require additional human and financial resources.

Basic palliative care training to all medical and nursing students has been the recommendation of the palliative

***Panel:* Strategies to extend palliative care during and after the COVID-19 pandemic**

Immediate responsiveness to adapt to pandemic parameters

Optimise cooperation and coordination

- Initiate formal and informal pathways for collective action and exchange by governments, bilateral and multilateral organisations, civil society, and the private sector based on the principle of solidarity.

Preserve continuity of care

- Ensure the availability and rational use of personal protective equipment and encourage self-care among palliative care health-care professionals and all caregivers.
- Ensure an adequate and balanced supply of opioid medication to all patients for relief of breathlessness and pain by instituting the simplified procedures of the International Narcotics Control Board.
- Conduct rapid training for all medical personnel to address additional palliative care needs of COVID-19 patients.
- Engage technology partners to equip community health workers with telehealth capabilities to virtually conduct home-based palliative care activities.
- Enable families to virtually visit and partake in health decisions with loved ones, especially at the end of life to address the almost universal fear of dying alone.

Enhance social support

- Enlist informal networks of community-based and faith-based organisations to mobilise and train a citizen volunteer workforce that is ready and able to teleconnect with patients in need of basic social support, delivering on palliative care's cornerstone feature—compassionate care.

Assess emerging needs

- Link with contact tracing activities and testing sites to collect data from the general public to better understand the social dimension of pandemic suffering.

Long-term preparedness strategies that embed palliative care into the core of medicine

- Expand all medical, nursing, social work, and community health worker curricula, as well as training of clergy, to include core palliative care competencies.
- Establish standard and resource-stratified palliative care guidelines and protocols for different stages of a pandemic and based on rapidly evolving situations and scenarios.

Delayed versus early initiation of renal replacement therapy for severe acute kidney injury: a systematic review and individual patient data meta-analysis of randomised clinical trials

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Summary

Background The timing of renal replacement therapy (RRT) for severe acute kidney injury is highly debated when no life-threatening complications are present. We assessed whether a strategy of delayed versus early RRT initiation affects 28-day survival in critically ill adults with severe acute kidney injury.

Methods In this systematic review and individual patient data meta-analysis, we searched MEDLINE (via PubMed), Embase, and the Cochrane Central Register of Controlled Trials for randomised trials published from April 1, 2008, to Dec 20, 2019, that compared delayed and early RRT initiation strategies in patients with severe acute kidney injury. Trials were eligible for inclusion if they included critically ill patients aged 18 years or older with acute kidney injury (defined as a Kidney Disease: Improving Global Outcomes [KDIGO] acute kidney injury stage 2 or 3, or, where KDIGO was unavailable, a renal Sequential Organ Failure Assessment score of 3 or higher). We contacted the principal investigator of each eligible trial to request individual patient data. From the included trials, any patients without acute kidney injury or who were not randomly allocated were not included in the individual patient data meta-analysis. The primary outcome was all-cause mortality at day 28 after randomisation. This study is registered with PROSPERO (CRD42019125025).

Findings Among the 1031 studies identified, one study that met the eligibility criteria was excluded because the recruitment period was not recent enough, and ten (including 2143 patients) were included in the analysis. Individual patient data were available for nine studies (2083 patients), from which 1879 patients had severe acute kidney injury and were randomly allocated: 946 (50%) to the delayed RRT group and 933 (50%) to the early RRT group. 390 (42%) of 929 patients allocated to the delayed RRT group and who had available data did not receive RRT. The proportion of patients who died by day 28 did not significantly differ between the delayed RRT group (366 [44%] of 837) and the early RRT group (355 [43%] of 827; risk ratio 1·01 [95% CI 0·91 to 1·13], p=0·80), corresponding to an overall risk difference of 0·01 (95% CI −0·04 to 0·06). There was no heterogeneity across studies (I^2=0%; τ^2=0), and most studies had a low risk of bias.

Interpretation The timing of RRT initiation does not affect survival in critically ill patients with severe acute kidney injury in the absence of urgent indications for RRT. Delaying RRT initiation, with close patient monitoring, might lead to a reduced use of RRT, thereby saving health resources.

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Introduction

Acute kidney injury occurs in up to 50% of critically ill patients and is associated with high morbidity and mortality.[1–5] Renal replacement therapy (RRT) can rapidly correct life-threatening complications associated with acute kidney injury, such as severe hyperkalaemia, metabolic acidosis, or pulmonary oedema due to fluid overload. However, the appropriate circumstances for initiating RRT when severe complications are not present remain controversial and uncertain.[6] Early initiation of RRT can allow better control of metabolic abnormalities and other complications associated with increased mortality, but could needlessly expose patients to iatrogenic complications (hypotension, bleeding, infection, or hypothermia).[7] The deliberate deferral of RRT initiation can allow time for spontaneous renal function recovery, thereby obviating the need for RRT.

Previous observational studies and small randomised controlled trials have had important limitations and generated discordant conclusions.[8–10] For example, in earlier observational studies[9] comparing all patients who received RRT, whether early or late, patients who recovered from severe acute kidney injury without ever receiving RRT were excluded. Omission of these patients

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See Online for appendix

Research in context

Evidence before this study

Renal replacement therapy (RRT) is frequently used for the management of severe acute kidney injury in critically ill patients. Although it is life-saving in many situations, RRT can be associated with complications, and the appropriate timing of its initiation has been a subject of intense debate. We searched MEDLINE (via PubMed), Embase, and the Cochrane Central Register of Controlled Trials without language restriction for randomised trials evaluating different timing of RRT initiation in the context of acute kidney injury. Most of the evidence available from studies published between 2000 and 2010 came from observational studies. These older observational studies, as well as study-level meta-analyses including them, suggested a potential benefit for early RRT. However, these observational studies did not include patients with severe acute kidney injury who never received RRT, and such studies are not adequate for investigating early versus delayed RRT strategies. Randomised controlled trials comparing RRT initiation strategies are needed to adequately evaluate these approaches. Several trials on RRT initiation strategies have been published, the three largest of which (AKIKI, IDEAL-ICU, and ELAIN) yielded conflicting results. Although the ELAIN trial (2016) showed a better survival outcome with early RRT, AKIKI (2016) and IDEAL-ICU (2018) did not find a survival difference between early and delayed RRT initiation strategies.

Added value of this study

This patient-level meta-analysis of clinical trials provides adequate statistical power to detect modest but potentially clinically meaningful effects on mortality of early versus delayed RRT initiation strategies, both in the overall population and in prespecified subgroups. The included studies showed, with a high quality of evidence, no statistically significant difference in mortality up to day 28 (and subsequently) between delayed and early RRT initiation strategies in critically ill patients with severe acute kidney injury.

Implications of all the available evidence

In the absence of urgent indications (eg, life-threatening metabolic complication), initiation of RRT can be safely postponed. Because a delayed RRT initiation strategy entails less frequent usage of RRT, by definition, this approach could have the benefit of saving health resources.

constitutes a major selection bias, as this group might be more likely to have a good prognosis compared with those who undergo RRT.[11,12] Methodological rigour mandates the conduct of randomised clinical trials comparing early and delayed RRT initiation strategies, in which RRT is initiated only when prespecified criteria are met.[13] Several such trials have been done in the past decade; however, whether these trials had adequate statistical power to detect a clinically important reduction in mortality with either strategy is a matter of ongoing debate.

We did a systematic review and individual patient data meta-analysis to compare the effects of delayed versus early RRT initiation strategies on 28-day survival in a large population of critically ill adult patients with severe acute kidney injury.

Methods

Overview

This systematic review with individual patient data meta-analysis was registered on PROSPERO (CRD42019125025) and followed a prespecified analysis plan. This study is reported in accordance with the Preferred Reporting Items for a Review and Meta-analysis of Individual Participant Data.[14]

Eligibility criteria

Eligible trials had to include critically ill patients aged 18 years or older, with severe acute kidney injury, defined as Kidney Disease: Improving Global Outcomes [KDIGO] acute kidney injury stage 2 or 3,[15] or (where KDIGO was unavailable) a renal Sequential Organ Failure Assessment (SOFA) score of 3 or higher. Trials were required to compare the effect of delayed versus early RRT initiation strategies on mortality in randomly allocated groups. We included trials published since Jan 1, 2009, as continuous progress in critical care quality has resulted in considerable improvement in the prognosis of patients with sepsis or multiorgan failure (which are often associated with severe acute kidney injury).[16,17] There were no language restrictions.

From the included trials, any patients without acute kidney injury or who were not randomly allocated were not included in the individual patient data meta-analysis. We did not include trials with patient enrolment before Jan 1, 2000.

Search strategy and selection process

We did an electronic search from April 1, 2008, to Dec 20, 2019, of the following databases: MEDLINE (via PubMed), Embase, and the Cochrane Central Register of Controlled Trials. We used keywords and free-text words related to acute kidney injury, renal replacement therapy, intensive care unit, as well as the sensitive filter developed by Cochrane to identify randomised controlled trials. The search algorithm for PubMed is reported in the appendix (p 2). We also searched ClinicalTrials.gov and the International Clinical Trial Registry Platform for completed and ongoing trials. In addition, we hand-searched conference proceedings of the American Thoracic Society, the Society of Critical Care Medicine, the European Society of Intensive Care Medicine, and the International Symposium on Intensive Care and Emergency Medicine since Jan 1, 2014. Finally, we

checked the reference lists of identified articles, recent editorials, and related reviews, and contacted experts to identify further eligible trials. Two investigators (NB and KC) independently screened the titles and abstracts to ascertain whether each study met the eligibility criteria. The full texts of the identified eligible articles were then evaluated to determine whether they should be included in the analysis. Disagreements between the two reviewers were resolved by consensus. In case of persistent disagreement, arbitration by a third reviewer (SG) settled the discrepancy.

Data collection and risk of bias assessment

We contacted the principal investigator of each eligible trial to request individual patient data in anonymised electronic datasets. We re-analysed each trial to check data and ensure reproducibility of results, in collaboration with each principal investigator and data manager. After evaluating data consistency and completeness and baseline imbalance (for risk of bias assessment), we confirmed the results of each trial and resolved all queries. We also reviewed the individual study protocols, template case report forms, and database dictionaries to harmonise study databases. Each database was updated with unified coding across trials and merged into a single database.

Two investigators (NB and KC) independently assessed the risk of bias of each included trial with the updated version of the Cochrane Risk of Bias Tool.[18] We evaluated risk of bias arising from the randomisation process (using full-text articles and individual patient data), due to deviation from the intended intervention (using full-text articles and protocols), due to missing outcome data (using full-text articles and individual patient data), in the measurement of outcome (using full-text articles and protocols), and in the selection of reported result (using full-text articles, protocols, and registration). We focused on our primary outcome for evaluation of risk of bias. Any discrepancy was solved by discussion and intervention of a third reviewer (AD) whenever necessary.

Each trial had been approved by a medical ethics committee according to the respective country's legislation, and all patients or their representatives were informed of the research at the time of inclusion. This individual patient data meta-analysis was approved by the medical ethics committee of Avicenne University Hospital (number CLEA-2019–99).

Outcomes

The primary outcome was all-cause mortality at day 28 after randomisation. Secondary outcomes were time to death (up to day 28), 60-day all-cause mortality, 90-day all-cause mortality, hospital mortality, duration of hospital stay, RRT-free days up to day 28, number of patients who did not receive RRT with the delayed strategy, RRT dependence at hospital discharge, serum creatinine concentration at hospital discharge in patients who no longer needed RRT, mechanical ventilation-free days up

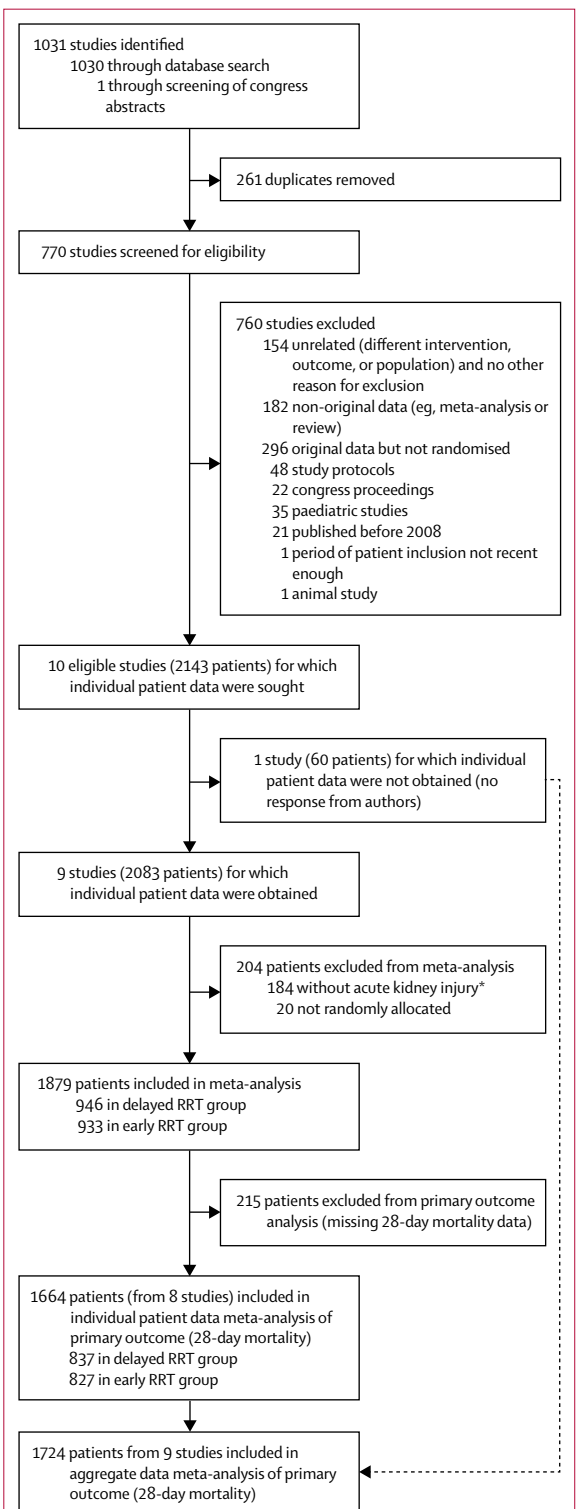

Figure 1: **Study profile**
RRT=renal replacement therapy. *Defined as Kidney Disease: Improving Global Outcomes acute kidney injury stage 2 or 3 (for HYPERDIA trial)[30] or Sequential Organ Failure Assessment score 3 or higher (for HEROICS trial).[29]

	Patients, n	Country	Recruitment period	Design and setting	Mean population age, years (SD)	Sex distribution (men, women)	Experimental RRT strategy	Criteria for RRT initiation		Time difference between RRT initiation strategies, h	RRT modality	Primary outcome
								Early strategy	Delayed strategy			
Jamale et al, 2013[28]	208	India	2010–12	Single-centre; medical population	Early 43 (15); delayed 42 (16)	68%, 32%	Early	Serum urea >25 mmol/L or serum creatinine >619 µmol/L	Refractory hyperkalaemia; volume overload; acidosis; uraemic nausea and anorexia (judged by consensus of two nephrologists)	NA	IHD	Hospital mortality
Wald et al, 2015 (STARRT)[25]	100	Canada	2012–13	Multicentre; mixed population	Early 62 (12); delayed 64 (14)	72%, 28%	Early	At least two of the following: 2-fold increase in serum creatinine from baseline; urine output <6 mL/kg in the preceding 12 h; whole-blood NGAL ≥400 ng/mL	Severe hyperkalaemia (>6 mmol/L); severe pulmonary oedema; severe metabolic acidosis (serum bicarbonate <10 mmol/L)	24	IHD, continuous RRT, sustained low-efficiency dialysis	90-day mortality
Combes et al, 2015 (HEROICS)[29]	224 (42)*	France	2009–12	Multicentre; cardiac surgery population	Early 61 (14); delayed 58 (16)	79%, 21%	Early	Persistent postoperative shock after cardiac surgery†	Life-threatening hyperkalaemia; KDIGO stage 3; serum urea >36 mmol/L	43	Continuous RRT	30-day mortality
Gaudry et al, 2016 (AKIKI)[22]	619	France	2013–16	Multicentre; mixed population	Early 65 (14); delayed 67 (13)	66%, 34%	Delayed	KDIGO stage 3‡	Severe hyperkalaemia (>6 mmol/L); severe pulmonary oedema refractory to diuretics; severe acidosis (pH <7·15); serum urea >40 mmol/L; oligo-anuria >72 h	55	IHD; continuous RRT	60-day mortality
Zarbock et al, 2016 (ELAIN)[24]	231	Germany	2013–15	Single-centre; surgical population	Early 66 (13); delayed 68 (13)	63%, 37%	Early	KDIGO stage 2§	KDIGO stage 3	20	Continuous RRT	90-day mortality
Barbar et al, 2018 (IDEAL-ICU)[23]	488	France	2012–16	Multicentre; mixed population	Early 69 (12); delayed 69 (13)	61%, 39%	Early	Failure stage of RIFLE¶	Severe hyperkalaemia (>6·5 mmol/L); severe pulmonary oedema refractory to diuretics; severe metabolic acidosis (pH <7·15); no renal function recovery after 48 h	45	IHD, continuous RRT	90-day mortality
Lumlertgul et al, 2018 (FST)[26]	118	Thailand	2016–17	Multicentre; mixed population	Early 67 (15); delayed 67 (17)	49%, 51%	Early	Acute kidney injury (any stage of KDIGO) and no response to furosemide stress test	Serum urea ≥100 mg/dL; severe hyperkalaemia (>6 mmol/L); severe metabolic acidosis (pH <7·15); severe pulmonary oedema	19	Continuous RRT	28-day mortality

(Table 1 continues on next page)

	Patients, n	Country	Recruitment period	Design and setting	Mean population age, years (SD)	Sex distribution (men, women)	Experimental RRT strategy	Criteria for RRT initiation		Time difference between RRT initiation strategies, h	RRT modality	Primary outcome
								Early strategy	Delayed strategy			
(Continued from previous page)												
Srisawat et al, 2018[27]	40	Thailand	2012–14	Multicentre; mixed population	All patients 69 (16)	55%, 45%	Early	Acute kidney injury, any RIFLE stage	Severe metabolic acidosis (pH <7·20); severe hyperkalaemia (>6·2 mmol/L); severe pulmonary oedema refractory to diuretics; persistent oliguria or anuria; serum urea >40 mg/dL	48	Continuous RRT	28-day mortality
Geri et al, 2019 (HYPERDIA)[30]	35 (33)*	France	2013–15	Single-centre; medical population	Early 58 (59–73); delayed 66 (65–72)	71%, 29%	Early	Post-cardiac arrest shock	Standard indications judged by physician in charge	NA	Continuous RRT	Delay to shock resolution
Xia et al, 2019[20]	60	China	2013–17	Single-centre; mixed population	Early 65 (12); delayed 67 (11)	55%, 45%	Early	Sepsis and urinary NGAL ≥1310 ng/mL	Severe hyperkalaemia (>6·5 mmol/L); severe pulmonary oedema; severe metabolic acidosis (pH <7·20)	NA	Continuous RRT	28-day mortality and RRT dependency

Individual patient data were obtained for all trials except Xia et al, 2019.[20] RRT=renal replacement therapy. NA=not available. IHD=intermittent haemodialysis. NGAL=neutrophil gelatinase-associated lipocalin. KDIGO=Kidney Disease: Improving Global Outcomes. RIFLE=Risk, Injury, Failure, Loss of renal function, and End-stage renal disease criteria. *Only patients with severe acute kidney injury (number in parentheses) were included in the meta-analysis. †Persistent postoperative shock was defined as requiring high dose catecholamines (epinephrine 0·2 mg/kg per min, norepinephrine. 0·4 mg/kg per min, or epinephrine + [norepinephrine/2] >0·2 mg/kg per min), or cardiovascular assistance using extracorporeal membrane oxygenation or extracorporeal life support within 3–24 hours after intensive care unit admission. ‡Serum creatinine ≥3 times baseline or increase ≥4 mg/dL (>353·6 µmol/L); or urine output <0·3 mL/kg per h for ≥24 h, or anuria for ≥12 h. §Serum creatinine 2·0–2·9 times baseline; or urine output <0·5 mL/kg per h for >12 h. ¶Serum creatinine ≥3 times baseline or increase ≥4 mg/dL (with acute rise >0·5 mg/dL); or urine output <0·3 mL/kg per h for ≥24 h, or anuria for ≥12 h.

Table 1: **Trial designs, patient characteristics, and definitions used in meta-analysed trials**

to day 28, and vasopressor-free days up to day 28. In addition, we assessed the rate of adverse events potentially related to acute kidney injury or to RRT: hyperkalaemia (>6·5 mmol/L), severe cardiac rhythm disorders (ventricular tachycardia, ventricular fibrillation, torsades de pointes, third-degree atrioventricular block, or extreme bradycardia requiring medical treatment), and severe bleeding events (bleeding requiring transfusion of at least 200 mL packed red blood cells or surgical control, or any intracranial bleeding).

All outcomes were prespecified except 90-day all-cause mortality.

Data analysis

Statistical analyses for all outcomes of interest were done with individual patient data, on an intention-to-treat basis. Treatment effects were expressed as risk ratios for binary outcomes, hazard ratios for time-to-event outcomes, and mean difference for quantitative outcomes. The analysis involved both one-step and two-step methods for the primary outcome and a two-step method for secondary outcomes. In the one-step method, we used a

	Delayed RRT group (n=946)	Early RRT group (n=933)
Age, years	64·3 (15·9); n=946	63·5 (15·4); n=933
Sex		
Male	609/946 (64%)	591/933 (63%)
Female	337/946 (36%)	342/933 (37%)
Main reason for admission		
Medical	294/509 (58%)	293/501 (58%)
Surgical	215/509 (42%)	208/501 (42%)
SOFA score	11·8 (3·7); n=914	11·7 (3·6); n=929
Coexisting conditions		
Chronic kidney disease	181/887 (20%)	135/896 (15%)
Hypertension	496/926 (54%)	480/913 (53%)
Diabetes	236/926 (25%)	226/913 (25%)
Sepsis	630/923 (68%)	623/913 (68%)
Diuretics at randomisation	221/801 (28%)	177/791 (22%)

Data are mean (SD) or n/N (%). RRT=renal replacement therapy. SOFA=Sequential Organ Failure Assessment.

Table 2: **Combined baseline characteristics from nine randomised clinical trials included in the individual patient data meta-analysis**

generalised linear mixed-effects model to analyse all trials simultaneously, accounting for the clustering of data within each trial with a random effect. In the two-step method, we first analysed separately each trial using individual patient data, before combining them using a random-effects meta-analysis model to account for variability between trials. Heterogeneity was evaluated by χ^2 test, I^2, and between-study variance (τ^2). To explore heterogeneity, we did subgroup analyses based on baseline characteristics: age (≤66 years or >66 years), sex, presence of sepsis at randomisation, presence of chronic kidney disease, and SOFA score at randomisation (≤12 or >12).[19] For quantitative characteristics, median values were used to dichotomise patients into subgroups. Interaction tests were done to evaluate whether the intervention effect varied between subgroups.

We planned sensitivity analyses for the primary outcome to account for risk of bias, by excluding trials at high or unclear risk of bias for each domain. In another sensitivity analysis, we accounted for one study for which individual patient data were not obtained[20] by extracting the number of events and number of patients analysed

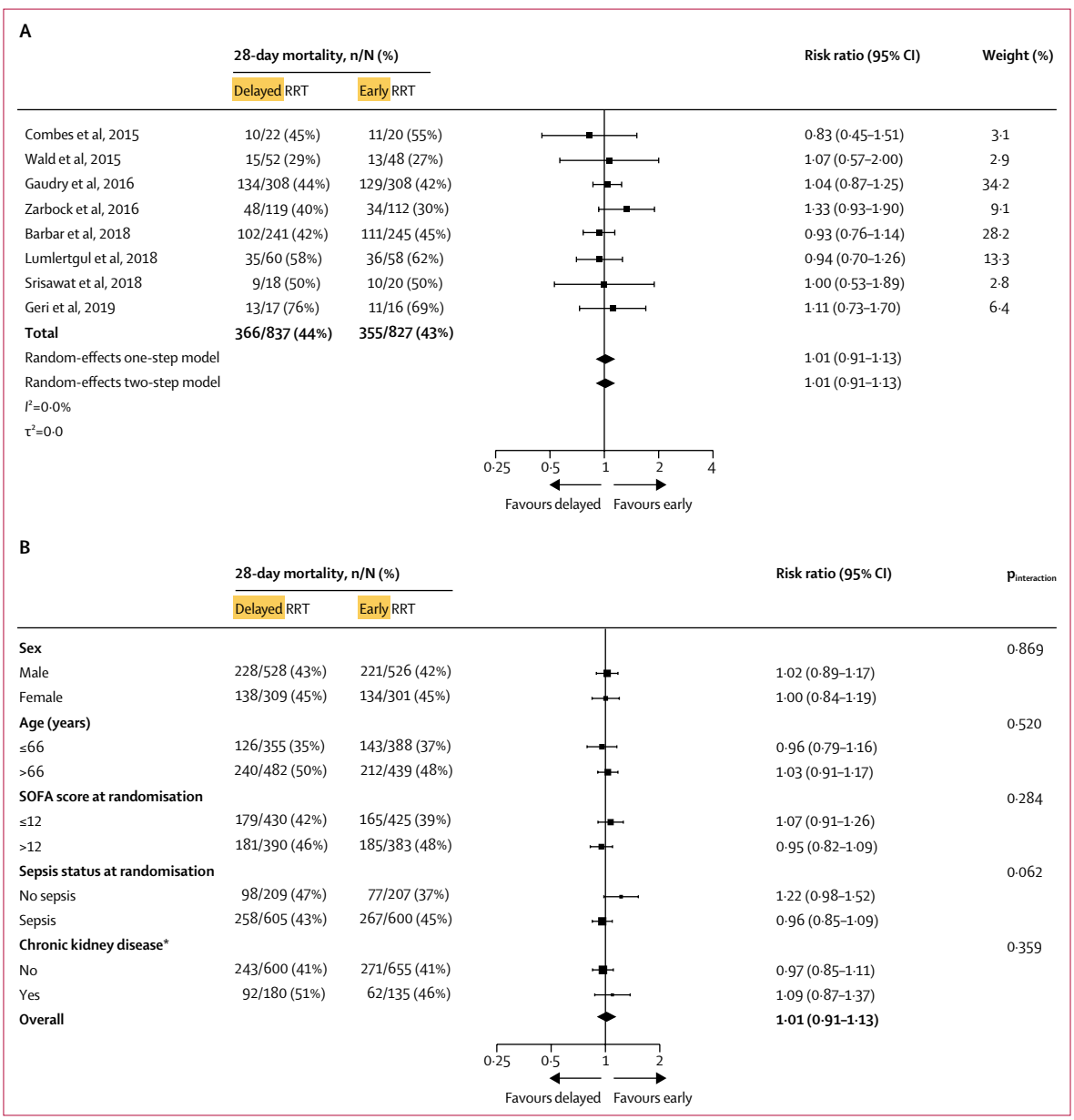

***Figure 2*: 28-day mortality among studies included in the individual patient data meta-analysis**
Forest plots show 28-day mortality by RRT initiation strategy in the intention-to-treat population among the overall sample (A), and among subgroups based on baseline characteristics (B). Data were available for eight[22–27,29,30] of the nine studies included in the individual patient data meta-analysis. SOFA=Sequential Organ Failure Assessment. RRT=renal replacement therapy. *Defined as a pre-existing creatinine clearance of less than 60 mL/min.

in each group for 28-day mortality from the article. We also did sensitivity analyses to account for differences in baseline prognostic factors between groups (with adjustment for age, sex, sepsis, chronic kidney disease, and SOFA score), and to account for missing primary outcome data (by multiple imputation and by worst and best case scenarios). Small study effect was evaluated with funnel plot.

We set the significance threshold at 5% (two-sided) for the primary outcome. For all secondary outcomes, we did not correct for multiple testing. As such, subgroup and sensitivity analyses should be considered as exploratory. All the analyses were done with the use of R software version 3.6.1.

Grading of evidence

The quality of evidence for the seven key outcomes (28-day mortality, 60-day mortality, 90-day mortality, hospital mortality, RRT-free days up to day 28, RRT dependence at hospital discharge, and severe bleeding events) was graded with GRADEpro Guideline Development Tool software.[11,19–26]

Role of the funding source

There was no funding source for this study.

Results

From the 1031 studies identified in our search, 261 duplicates were removed, and 770 titles and abstracts were screened for eligibility. One study published in 2009 that met the eligibility criteria was excluded because the enrolment period (1997–99) was not recent enough.[21] After full-text reviews, ten trials[20,22–30] (including a total of 2143 participants) were eligible for inclusion in the meta-analysis (figure 1): five done in Europe, four in Asia, and one in North America. Individual patient data were obtained from nine randomised trials[22–30] (2083 patients). We were unable to obtain individual patient data for one randomised trial (60 patients);[20] this study was accounted for in a sensitivity analysis (appendix p 6).

Trial and population characteristics and definitions used for early and delayed RRT strategies are shown in table 1. Most studies were at low risk of bias (appendix p 3). There was no masking for any subjective assessment in the studies.

In seven trials,[22–28] all included patients had severe acute kidney injury according to our inclusion criteria. In the two other trials, HEROICS[29] and HYPERDIA,[30] patients were included and randomly allocated irrespective of the presence of acute kidney injury, and we selected only patients with severe acute kidney injury (those with KDIGO acute kidney injury stage 2 or 3 in HYPERDIA,[30] and those with renal SOFA score ≥3 in HEROICS,[29] where KDIGO stage was unavailable). 33 of 35 patients from the HYPERDIA trial and 42 of 224 from the HEROICS trial were included in the individual patient data meta-analysis. In addition, in the trial by Srisawat and colleagues,[27] only 40 of 60 patients were randomly allocated and therefore included in the individual patient data meta-analysis (figure 1).

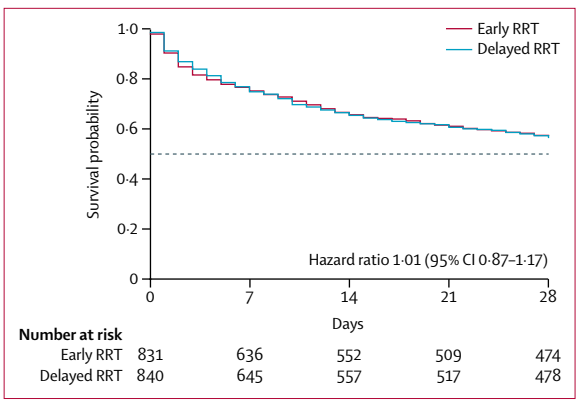

Figure 3: **Probability of survival up to day 28 in the intention-to-treat population according to RRT initiation strategy**
28-day survival data were available for eight[22–27,29,30] of the nine studies included in the individual patient data meta-analysis. RRT=renal replacement therapy.

The individual patient data meta-analysis included 1879 patients: 946 (50%) allocated to a delayed strategy group and 933 (50%) allocated to an early RRT strategy group. Baseline characteristics of these patients are presented in table 2.

Data on the prespecified primary outcome (28-day mortality) were not available for 215 patients, including all 208 patients in Jamale and colleagues' study,[28] which assessed mortality at hospital discharge only, and a further seven patients (four in the early RRT group and three in the delayed RRT group) among the eight other studies. Among the remaining 1664 patients, 366 (44%) of 837 patients in the delayed RRT group and 355 (43%) of 827 patients in the early RRT group died within 28 days of randomisation (risk ratio 1·01 [95% CI 0·91 to 1·13], p=0·80; figure 2A), corresponding to an overall risk difference of 0·01 (95% CI –0·04 to 0·06). There was no evidence of heterogeneity across trials (I^2=0·0%, τ^2=0·00; figure 2A). Funnel plots showed no major asymmetry (appendix p 10). Figure 3 shows the Kaplan-Meier estimate of the overall mortality up to day 28. The combined hazard ratio was 1·01 (95% CI 0·87 to 1·17) with no evidence of heterogeneity across trials (I^2=0%, τ^2=0).

Among the 929 patients allocated to the delayed RRT group for whom data were available, 390 (42%) never received RRT. However, RRT-free days up to day 28 did not significantly differ between the delayed RRT group (mean 13·1 days [SD 12·5]) and the early RRT group (12·0 days [11·7]; mean difference 1·0 days [95% CI –0·3 to 2·2], p=0·121). There were no significant between-group differences with respect to mortality at days 60 and 90, hospital mortality, duration of hospital stay, RRT dependence at hospital discharge, serum creatinine level at hospital discharge (among patients with no RRT dependence at discharge), mechanical ventilation-free days up to day 28, or vasopressor-free

	Outcome		Number of trials included (total patients)	Missing data*	Combined risk ratio or mean difference (95% CI)	I^2
	Delayed RRT group (n=946)	Early RRT group (n=933)				
28-day mortality	366/837 (44%)	355/827 (43%)	8 (n=1671)	7	1·01 (0·91 to 1·13)†	0·0%
Patients who never received RRT	390/929 (42%)	NA	9 (n=946)	17	NA	..
60-day mortality	407/799 (51%)	398/784 (51%)	6 (n=1598)	15	0·99 (0·90 to 1·09)†	0·0%
90-day mortality	267/485 (55%)	260/467 (56%)	5 (n=979)	27	0·98 (0·83 to 1·16)†	45·2%
Hospital mortality	412/891 (46%)	417/881 (47%)	7 (n=1806)	34	0·98 (0·89 to 1·08)†	0·0%
Length of hospital stay, days	32·7 (43·9); n=898	29·6 (40·4); n=891	7 (n=1806)	17	1·8 (–3·2 to 6·7)‡	61·2%
RRT-free days	13·0 (12·5); n=676	12·0 (11·7); n=687	6 (n=1407)	44	1·0 (–0·3 to 2·2)‡	0·0%
RRT dependence at hospital discharge	39/328 (12%)	31/341 (9%)	4 (n=689)	20	1·34 (0·72 to 2·47)†	40·5%
Serum creatinine before hospital discharge (μmol/L)						
All patients	115·3 (113·3); n=440	129·3 (119·5); n=391	8 (n=962)	131	4·4 (–21·8 to 30·7)‡	73·5%
Patients free of RRT at hospital discharge	108·1 (74·0); n=263	120·2 (93·7); n=285	4 (n=599)	51	–15·9 (–39·4 to 7·5)‡	58·2%
Mechanical ventilation-free days	8·8 (10·7); n=622	9·0 (10·7); n=627	5 (n=1707)	58	–0·2 (–1·6 to 1·1)‡	11·0%
Vasopressor-free days	13·3 (12·0); n=571	13·4 (12·0); n=576	3 (n=1149)	2	–0·0 (–1·4 to 1·4)‡	0·0%

Outcome data are mean (SD) or n/N (%). All outcomes were prespecified except 90-day mortality. RRT=renal replacement therapy. NA=not applicable. *Number of patients with missing data among the trials included in the analysis of each outcome. †Risk ratio (binary outcomes). ‡Mean difference (quantitative outcomes).

Table 3: **Primary and secondary outcomes in the intention-to-treat population**

	Adverse events, n/N (%)		Number of trials included (total patients)	Missing data*	Risk ratio (95% CI)	I^2
	Delayed RRT group (n=946)	Early RRT group (n=933)				
Hyperkalaemia	29/567 (5%)	20/573 (3%)	3 (n=1149)	9	1·52 (0·20–11·45)	72·4%
Severe cardiac rhythm disorder	73/792 (9%)	61/795 (8%)	6 (n=1598)	11	1·20 (0·71–2·01)	49·6%
Severe bleeding events	111/790 (14%)	96/785 (12%)	6 (n=1575)	0	1·15 (0·90–1·48)	0·0%

RRT=renal replacement therapy. *Number of patients with missing data among the trials included in the analysis of each outcome.

Table 4: **Adverse events in the intention-to-treat population**

days up to day 28 (table 3). Furthermore, risk of adverse events (hyperkalaemia, severe cardiac rhythm disorder, and severe bleeding events) did not significantly differ between groups (table 4).

Quality of evidence is summarised in the appendix (p 4). The quality of evidence was high for the following outcomes: 28-day mortality, 60-day mortality, hospital mortality, and RRT-free days up to day 28. 90-day mortality and frequency of severe bleeding events had a moderate quality of evidence, and RRT dependence at discharge had a low quality of evidence.

All sensitivity analyses of the primary outcome confirmed the results of the main analysis (appendix pp 6–9). In subgroup analyses of the primary outcome, no statistically significant interactions between baseline characteristics and treatment effect were seen (figure 2B).

Discussion

Our individual patient data meta-analysis showed no significant differences in mortality rate at day 28 and beyond according to the timing of RRT initiation. A strategy of early RRT initiation did not confer any tangible clinical benefits for patients in the studies analysed. These results were robust when analysing 28-day mortality as a censored variable and also in all sensitivity analyses, including the aggregated data analysis accounting for one study that did not provide individual patient data. These findings help to inform one of the most controversial issues in critical care nephrology.

Previously, most knowledge on the relationship between RRT timing and clinical outcomes came from observational studies and meta-analyses of these studies. This evidence suggested a benefit of early RRT; however, those studies were likely to be biased as they only included patients who actually received RRT, while patients with severe acute kidney injury who recovered kidney function without ever receiving RRT—and who might have otherwise had an excellent prognosis—were generally not considered.[11,12] Data from larger randomised trials in recent years has significantly expanded the evidence base, but yielded discrepant results.[12,23,24] Although there have been meta-analyses that included patients enrolled in these trials, to our knowledge, the current meta-analysis is the first to use individual patient-level data. In addition, most previous meta-analyses[8,31–33] did not include the most recent studies, and all included older trials that might no longer be relevant in the context of critical care.[8,31–34]

We chose to restrict our meta-analysis to trials involving patients treated in the past 10 years to reflect only those exposed to contemporary care. Continuous improvement

in the outcomes of critically ill patients[16,17] has undoubtedly affected the prognosis of patients with severe acute kidney injury, which is often associated with failure of other organs or sepsis. For instance, mortality due to acute respiratory distress syndrome decreased by 9% between 1996 and 2013, and mortality due to septic shock decreased by 25% between 1989 and 2010.[16,17]

Individual patient data meta-analyses provide a better level of evidence than other types of meta-analyses because they are not affected by poor quality of reporting in articles—a major threat to aggregated data meta-analyses—and they allow better evaluation of survival outcomes and exploration of heterogeneity in treatment effect with subgroup analyses. In addition, availability of individual patient data can allow for the selection of patients from trials that meet the eligibility criteria of the wider population in the meta-analysis.[29,30]

To be relevant, individual patient data meta-analyses need to include individual patient data for most eligible studies identified through a systematic review, which was the case in our study. We included the trial by Jamale and colleagues,[28] which was not strictly restricted to the setting of critical care units, but nevertheless included a population of patients with severe acute kidney injury, 80% of whom had dysfunction of at least one non-renal organ. We were able to obtain data for nine of the ten eligible studies, representing 97% of all eligible patients. Only one small study (n=60) with a higher risk of bias did not provide individual patient data,[20] but our results were consistent when accounting for this study in a sensitivity analysis.

Our meta-analysis included individual data for 1879 patients, 1664 of whom were included in primary outcome analysis. This large sample was composed of a mixed population of patients (medical and surgical) with many different diagnoses and organ failures at admission, and thus encompasses the variety of disorders encountered in critically ill patients.

By definition, a delayed RRT strategy leads to fewer patients receiving RRT, either because death occurs before RRT initiation criteria are met or because renal recovery obviates the need for RRT. In this meta-analysis, 42% of patients allocated to the delayed strategy did not receive RRT, suggesting that broader adoption of the delayed strategy might translate into reduced use of health resources. However, the delayed strategy did not result in fewer RRT-free days compared with the early RRT group. This finding might be explained by the competing risk of death: non-survivors at day 28 were attributed a zero value for RRT-free days, which decreases the power of this comparison when mortality is high.[35]

Notably, each adverse event (hyperkalaemia, severe bleeding, and severe cardiac rhythm disorder) was infrequent and its incidence did not significantly differ between delayed and early strategies. Therefore, postponing RRT might be safe in the absence of life-threatening conditions.

In our subgroup analyses based on baseline patient characteristics, severity of illness on admission (SOFA score) did not affect the results, and no significant interaction between the presence of chronic kidney disease and treatment effect was evident. These results conflict with those of a post-hoc analysis[36] of a previous trial,[22] which suggested that patients with chronic kidney disease might have a higher risk of mortality with early RRT. Relative risks in patients with and without sepsis ruled out a possible heterogeneity of the treatment effect: the comparison between these two subgroups yielded a $p_{interaction}$ of 0·062, although no correction was done to account for multiplicity of comparisons. The STARRT-AKI trial (NCT02568722) is now completed, having enrolled 3000 patients who were randomly allocated to different RRT initiation strategies, and will examine the effects of sepsis and mortality, in addition to other issues.[37] STARRT-AKI will also provide information on long-term quality of life.

The strengths of this meta-analysis include the comprehensive search strategy and retrieval of all relevant trials, most of which had a low risk of bias, as well as the inclusion of individual data from almost all trials, the very small amount of unavailable data for the primary outcome, and the focus on recent intensive care unit research. However, there were several limitations. In particular, the included trials had different definitions for what constituted early and delayed RRT initiation strategies. Most studies[22–26] reported a delay of 2–8 h for initiating RRT after randomisation in the early strategy. By contrast, defining the delayed strategy is more difficult, as some studies used a fixed objective criterion (eg, reaching a more severe stage of acute kidney injury[24] or a fixed number of days[23]), whereas others based the decision to start RRT on the occurrence of metabolic complications.[22,23,25] Therefore, there was noticeable variation in the timing of delayed RRT, from 25 h[24] to 57 h.[22] An ongoing randomised trial[38] is examining the possibility of further extending the delay in RRT initiation.

In summary, this individual patient data meta-analysis shows that mortality does not differ significantly according to whether RRT is initiated early or delayed in patients with acute kidney injury. The deliberate delay of RRT initiation under close patient supervision, and the initiation only when a clinical indication emerges, appears to be an acceptable approach, with the potential for resource savings.

Contributors

SG, DH, AD, J-PQ, and DD conceived the study and wrote the initial protocol and the manuscript. SG, NB, KC, and AD did the literature search. DH and AD did the statistical analysis. All authors shared trial data, gave crucial feedback on the protocol, and provided critical revision for and approved the final version of the manuscript.

Declaration of interests

NB is the recipient of a grant from the Société Francophone de Néphrologie, Dialyse et Transplantation, for the submitted work. AZ reports grants and personal fees from Baxter, grants from Fresenius,

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