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Timing of kidney replacement therapy initiation for acute kidney injury (Review)

Fayad AI, Buamscha DG, Ciapponi A

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[Intervention Review]

Timing of kidney replacement therapy initiation for acute kidney injury

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ABSTRACT

Background

Acute kidney injury (AKI) is a common condition among patients in intensive care units (ICUs) and is associated with high numbers of deaths. Kidney replacement therapy (KRT) is a blood purification technique used to treat the most severe forms of AKI. The optimal time to initiate KRT so as to improve clinical outcomes remains uncertain. This is an update of a review first published in 2018.

This review complements another Cochrane review by the same authors: *Intensity of continuous renal replacement therapy for acute kidney injury*.

Objectives

To assess the effects of different timing (early and standard) of KRT initiation on death and recovery of kidney function in critically ill patients with AKI.

Search methods

We searched the Cochrane Kidney and Transplant's Specialised Register to 4 August 2022 through contact with the Information Specialist using search terms relevant to this review. Studies in the Register are identified through searches of CENTRAL, MEDLINE, EMBASE, conference proceedings, the International Clinical Trials Register, ClinicalTrials and LILACS to 1 August 2022.

Selection criteria

We included all randomised controlled trials (RCTs). We included all patients with AKI in the ICU regardless of age, comparing early versus standard KRT initiation. For safety and cost outcomes, we planned to include cohort studies and non-RCTs.

Data collection and analysis

Data were extracted independently by two authors. The random-effects model was used, and results were reported as risk ratios(RR) for dichotomous outcomes and mean difference(MD) for continuous outcomes, with 95% confidence intervals (CI).

Main results

We included 12 studies enrolling 4880 participants. Overall, most domains were assessed as being at low or unclear risk of bias.

Compared to standard treatment, early KRT initiation may have little to no difference on the risk of death at day 30 (12 studies, 4826 participants: RR 0.97,95% CI 0.87 to 1.09; I^2= 29%; low certainty evidence), and death after 30 days (7 studies, 4534 participants: RR 0.99, 95% CI 0.92 to 1.07; I^2 = 6%; moderate certainty evidence).

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Early KRT initiation may make little or no difference to the risk of death or non-recovery of kidney function at 90 days (6 studies, 4011 participants: RR 0.91, 95% CI 0.74 to 1.11; I^2 = 66%; low certainty evidence); CIs included both benefits and harms.

Low certainty evidence showed early KRT initiation may make little or no difference to the number of patients who were free from KRT (10 studies, 4717 participants: RR 1.07, 95% CI 0.94 to1.22; I^2 = 55%) and recovery of kidney function among survivors who were free from KRT after day 30 (10 studies, 2510 participants: RR 1.02, 95% CI 0.97 to 1.07; I^2 = 69%) compared to standard treatment.

High certainty evidence showed early KRT initiation increased the risk of hypophosphataemia (1 study, 2927 participants: RR 1.80, 95% CI 1.33 to 2.44), hypotension (5 studies, 3864 participants: RR 1.54, 95% CI 1.29 to 1.85; I^2 = 0%), cardiac-rhythm disorder (6 studies, 4483 participants: RR 1.35, 95% CI 1.04 to 1.75; I^2 = 16%), and infection (5 studies, 4252 participants: RR 1.33, 95% CI 1.00 to 1.77; I^2 = 0%); however, it is uncertain whether early KRT initiation increases or reduces the number of patients who experienced any adverse events (5 studies, 3983 participants: RR 1.23, 95% CI 0.90 to 1.68; I^2 = 91%; very low certainty evidence).

Moderate certainty evidence showed early KRT initiation probably reduces the number of days in hospital (7 studies, 4589 participants: MD-2.45 days, 95% CI -4.75 to -0.14; I^2 = 10%) and length of stay in ICU (5 studies, 4240 participants: MD -1.01 days, 95% CI -1.60 to -0.42; I^2 = 0%).

Authors' conclusions

Based on mainly low to moderate certainty of the evidence, early KRT has no beneficial effect on death and may increase the recovery of kidney function. Earlier KRT probably reduces the length of ICU and hospital stay but increases the risk of adverse events.

Further adequate-powered RCTs using robust and validated tools that complement clinical judgement are needed to define the optimal time of KRT in critical patients with AKI in order to improve their outcomes. The surgical AKI population should be considered in future research.

PLAIN LANGUAGE SUMMARY

Timing of initiation of kidney replacement therapy (dialysis) for acute kidney injury

What is the issue?

Acute kidney injury (AKI) is very common among patients admitted to the intensive care unit (ICU); it is associated with high death rates and is characterised by the rapid loss of kidney function. Patients with AKI show increased levels of serum uraemic toxins (creatinine and urea), serum potassium and metabolic acids, accumulation of fluid and, in most cases, a reduction in urine output. In this population, these chemicals and fluid overload are related to increased rates of death. Theoretically, early removal of toxins and excess fluid from the bloodstream might improve patient outcomes (such as death rate and recovery of kidney function).

Kidney replacement therapy (KRT), also known as dialysis, is a blood purification technique that enables the removal of excess fluid and toxins. KRT involves blood being diverted from the patient via a catheter (a hollow, flexible tube placed into a vein) through a filtering system which removes excess fluid and toxins; purified blood is then returned to the patient via the catheter. Early initiation of KRT improves the removal of toxins and excess fluid.

The aim of this review was to investigate the effect of the different timing of KRT initiation (early or standard) on death, recovery of kidney function, and adverse events in people with AKI who are critically ill.

What did we do?

We searched the literature up until 4 August 2022 and identified 12 studies enrolling 4880 critically ill patients with AKI that were evaluated in this review.

What did we find?

Compared to standard, early KRT initiation may have no benefits on death; however, may increase recovery of kidney function and probably reduces the number of days in ICU and hospital stay, but increases the risk of adverse events in patients with AKI in intensive care units. Nevertheless, regarding death and recovery of kidney function, early KRT initiation showed a range of values that included benefits as well as harms.

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Summary of findings 1. Early versus standard initiation of kidney replacement therapy (KRT) in patients with acute kidney injury (AKI)

Early versus standard initiation of KRT in patients with AKI

Patient or population: AKI
Setting: intensive care unit
Intervention: early initiation
Comparison: standard initiation

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (RCTs)	Certainty of the evidence (GRADE)
	Risk with standard initiation	Risk difference with early initiation			
Death at day 30	385 per 1000	12 fewer per 1000 (50 fewer to 35 more)	RR 0.97 (0.87 to 1.09)	4826 (12)	⊕⊕⊖⊖ Low [1,2]
Death after 30 days	457 per 1000	5 fewer per 1000 (37 fewer to 32 more)	RR 0.99 (0.92 to 1.07)	4534 (7)	⊕⊕⊕⊖ Moderate[1]
Death or non-recovery of kidney function **Time frame: day 90**	468 per 1000	42 fewer per 1000 (122 fewer to 51 more)	RR 0.91 (0.74 to 1.11)	4011(6)	⊕⊕⊖⊖ Low [1,2]
Recovery of kidney function **Patients free from KRT according to ITT analysis (all patients)**	493 per 1000	34 more per 1000 (30 fewer to 108 more)	RR 1.07 (0.94 to 1.22)	4717 (10)	⊕⊕⊖⊖ Low [1,2]
Adverse events: hypophosphataemia	42 per 1000	34 more per 1000 (14 more to 61 more)	RR 1.80 (1.33 to 2.44)	2927 (1)	⊕⊕⊕⊕ High
Adverse events: hypotension	81 per 1000	44 more per 1000 (23 more to 69 more)	RR 1.54 (1.29 to 1.85)	3864 (5)	⊕⊕⊕⊕ High
Adverse events: cardiac-rhythm disorder	54 per 1000	19 more per 1000 (2 more to 41 more)	RR 1.35 (1.04 to 1.75)	4483 (6)	⊕⊕⊕⊕ High
Adverse events: infection	33 per 1000	11 more per 1000 (0 fewer to 25 more)	RR 1.33 (1.00 to 1.77)	4252 (5)	⊕⊕⊕⊕ High

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Length of stay in ICU	Mean length of stay in ICU was 1.01 days less with early initiation (1.6 less to 0.42 less) compared to standard initiation	-	4240 (5)	⊕⊕⊕⊖ Moderate[3]
Length of stay in hospital	The mean length of stay in hospital was 2.45 days less with early initiation (4.75 less to 0.14 less) compared to standard initiation	-	4589 (7)	⊕⊕⊕⊖ Moderate [3]

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio; **MD:** mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1] Imprecision: due to the CI crossed the threshold for clinically meaningful effects
[2] Inconsistency: due to heterogeneity
[3] Indirectness: critically ill patients with AKI in RKT have high short-term risk of death; death is a competing end point for kidney recovery at day 90

Summary of findings 2. Subgroup analyses: early versus standard initiation of kidney replacement therapy (KRT) in patients with acute kidney injury (AKI)

Early versus standard initiation of KRT in patients with AKI

Patient or population: AKI
Setting: intensive care unit
Intervention: early initiation
Comparison: standard initiation

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (RCTs)	Certainty of the evidence (GRADE)
	Risk with standard initiation	Risk difference with early initiation			
Death by AKI aetiology: non-surgical causes	383 per 1000	4 more per 1000 (23 fewer to 34 more)	RR 1.01 (0.94 to 1.09)	4461 (9)	⊕⊕⊕⊖ Moderate [2]
Death by AKI aetiology: surgical causes	408 per 1000	143 fewer per 1000 (282 fewer to 147 more)	RR 0.65 (0.31 to 1.36)	365 (3)	⊕⊕⊖⊖ Low [1 2]

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Kidney recovery functionby KRT: continuous KRT	355 per 1000	149 more per 1000 (4 fewer to 365 more)	RR 1.42 (0.99 to 2.03)	583 (6)	⊕⊕⊕⊖ Moderate[2]
Kidney recovery functionby KRT: continuous and intermittent KRT	520 per 1000	21 fewer per 1000 (47 fewer to 10 more)	RR 0.96 (0.91 to 1.02)	4134 (4)	⊕⊕⊕⊖ Moderate [1]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio; **KRT**: kidney replacement therapy

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1] Imprecision: due to the CI crossed the threshold for clinically meaningful effects
[2] Inconsistency: due to heterogeneity

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BACKGROUND

Description of the condition

Acute kidney injury (AKI) is a complex clinical entity characterised by an abrupt decline in kidney function (Mehta 2007). AKI incidence among adults admitted to intensive care units (ICUs) ranges from 5% to 20% (Joannidis 2005); in children, the incidence is 10% (Schneider 2010). Despite its potential to be reversed, AKI is associated with high rates of morbidity and death (Bagshaw 2007). Kidney replacement therapy (KRT) has become a form of kidney support for critically ill patients with AKI (Wald 2015). Despite advances in clinical care and KRT, the presence of AKI in the ICU setting is associated with poor prognosis and requires significant healthcare resources (Sutherland 2010; Uchino 2005).

Description of the intervention

KRT is an extracorporeal blood purification therapy intended to support impaired kidney function. We included the following KRT modalities: Continuous KRT (CKRT) slowly removes fluid (Foland 2004; Gibney 2008; Goldstein 2001) and high to small molecular weight solutes efficiently over prolonged periods (Brunnet 1999; Clark 1999; Liao 2003; Sieberth 1995), and confers beneficial haemodynamic stability effects. CKRT modalities are defined by their main solute clearance mechanism. These are convection (continuous venovenous haemofiltration (CVVHF), diffusion (continuous venovenous haemodialysis (CVVHD), or a combination of both convection and diffusion (continuous venovenous haemodiafiltration, CVVHDF) (Palevsky 2002). The intermittent KRT (IKRT) removes fluid and lower molecular weight solutes over a short period of time (sessions of three to five hours), two or three times a week. Diffusion is the main solute clearance mechanism. These are intermittent haemodialysis (IHD), intermittent haemofiltration (IHF), intermittent haemodiafiltration (IHDF), and intermittent high-flux dialysis (IHFD). The hybrid therapies, also known as prolonged IKRTs, such as sustained low-efficiency dialysis (SLED) and extended-duration dialysis (EDD); provides KRT for an extended period of time (six to 18 hours), at least three times/week (Edrees 2016); includes both convective (i.e. haemofiltration) and diffusive (i.e. haemodialysis) therapies, depending on the method of solute removal (Marshall 2011). Peritoneal dialysis modality was not included.

Timing of KRT initiation is generally related to "when to start renal support in critically ill patients with AKI". A number of organisations have published practice guidelines that include statements on the timing of KRT initiation in ICU settings. The Kidney Disease Improving Global Outcomes (KDIGO 2012), the National Institute for Health and Care Excellence (NICE 2013) and the French Intensive Care Society (Vinsonneau 2015) have published practice guidelines that include statements on the timing of KRT initiation in ICU settings. There has been consensus on the standard initiation criteria: when life-threatening changes in fluid, electrolytes and acid-based balance exist according to different guidelines; however, none of the recommendations have been graded. Unfortunately, there has been little consensus on the early beginning of KRT in ICU patients with AKI. Some published studies have used urine output and serum creatinine (SCr) (Sugahara 2004) or urine output and creatinine clearance (CrCl) (Bouman 2002) as surrogate criteria of early initiation. Other authors have considered time to ICU admission (Bagshaw 2009), time to fulfilling AKI stage 2 within 8 hr (ELAIN 2016) or within 12 hr using a novel kidney damage biomarker neutrophil gelatinase-associated lipocalin (NGAL) (EARLYRRT 2018; STARRT-AKI Pilot 2013; Xia 2019), and time to fulfilling AKI stage 3 (AKIKI 2015). With poor agreement (expert opinion), NICE 2013 and Vinsonneau 2015 also published possible indicators for early kidney support therapy, e.g. weight "gain less than 10%, urea less than 25 mmol/litre and oliguria 0.5 ml/kg/hr or less for at least 24 hours" or "KDIGO AKI stage 2 or within 24 hr after the onset of AKI of which reversibility seems unlikely, respectively". In our review, we will assign definitions given in included studies in relation to early and standard KRT initiation.

How the intervention might work

A hypothesis that the timing of KRT commencement may affect survival emerged from animal and human studies over the past decade. Animal studies investigating sepsis (Mink 1995) and pancreatitis (Yekebas 2002) suggested beneficial effects on physiologic and clinical endpoints when haemofiltration was started early, simultaneously or two hours after injury. Several observational studies investigated the effect of timing in patients with AKI; Teschan 1960 reported improved survival rates relating to KRT timing in patients commencing dialysis with low blood urea nitrogen; Gettings 1999 indicated improved survival in early haemofiltration patients with AKI related to trauma, the same was found in patients with AKI post cardiac surgery (Bouman 2002; Demirkilic 2004; Elahi 2004; Sugahara 2004). Randomised controlled trials (RCTs) found patients with pancreatitis had significantly better survival in patients who received early haemofiltration (within 48 hours after the onset of abdominal pain) than in the group with late haemofiltration (96 hours after the onset of abdominal pain (Jiang 2005), while other RCTs failed to demonstrate these advantages (AKIKI 2015; STARRT-AKI Pilot 2013; STARRT-AKI 2019).

Why it is important to do this review

Studies assessing KRT timing (early versus standard) have reported inconsistent results: earlier studies indicated significant improvements in survival and kidney function recovery, yet others, including RCTs and meta-analyses, did not find these benefits. We investigated the relationship between different timing of KRT initiation and clinical outcomes for critical patients with AKI. Review evidence could have direct relevance to guide clinical practice.

This review complements another Cochrane systematic review by the same authors: *Intensity of continuous renal replacement therapy for acute kidney injury* (Fayad 2016).

OBJECTIVES

To assess the effects of different timing (early and standard) of KRT initiation on death and recovery of kidney function in critically ill patients with AKI.

METHODS

Criteria for considering studies for this review

Types of studies

All RCTs looking at KRT modalities for people with AKI in ICU settings were eligible for inclusion. For outcomes such as safety and costs, non-RCTs and cohort studies were also planned to be included if sufficiently high quality, sampling was clearly described,

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patients characterised, proportions of patients experiencing any adverse events or who dropped out because of adverse events were adequately reported, co-interventions were described, and at least 80% of patients included were analysed after treatment.

Types of participants

Inclusion criteria

We included all patients with AKI in the ICU being treated with KRT regardless of age and gender. We assigned AKI definitions cited by the included studies.

Exclusion criteria

We excluded patients who received dialysis treatment before admission to ICU, patients admitted for drug overdose (doses exceeding therapeutic requirements), or with acute poisoning (all toxins).

Types of interventions

We compared early (intervention group) versus standard (control) initiation in CKRT and IKRT. We excluded the peritoneal dialysis modality. The criteria of time were defined as published in the original publications.

Types of outcome measures

Primary outcomes

Death

- Death from any cause at days 7, 15, 30, 60 and 90
- Death or non-recovery of kidney function at day 90.

Recovery of kidney function

- Number free of KRT according to intention-to-treat analysis
- Number free of KRT according to intention-to-treat analysis at days 30, 60 and 90.

Secondary outcomes

Adverse events

- Number experiencing any adverse events
- Number who dropped out because of any adverse events (technique or patient-dependent factors)
- Number with intervention-related complications (e.g. disequilibrium, hypokalaemia, hypophosphataemia, hypocalcaemia, bleeding, hypotension)
- Number with catheter-related complications.

We looked for differences in overall drop-out rates and any adverse effects by type (mild or severe). We defined adverse events severity where medical therapeutic interventions were implied in reporting. Withdrawals due to protocol violation or loss to follow-up were not included in counts of adverse events.

Length of stay

- Days in hospital
- Days in ICU.

Cost

We planned to assess the costs of KRT modalities, including:

- Type and number of dialyser filters
- Use or no use of anticoagulation
- Types of anticoagulation and anticoagulants
- Use of replacement fluid
- Number of days on KRT.

All costs were to be reported in international monetary units.

- Cost/day of KRT
- Length of hospital stay with KRT
- Length of ICU stay with KRT.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Kidney and Transplant Specialised Register to 4 August 2022 through contact with the Information Specialist using search terms relevant to this review. The Specialised Register contains studies identified from the following sources.

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of kidney-related journals and the proceedings of major kidney conferences
4. Searching the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney and transplant journals
6. Searches of the International Clinical Trials Register (ICTRP). Search Portal and ClinicalTrials.gov.

Studies contained in the Specialised Register were identified through search strategies for CENTRAL, MEDLINE and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of these strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available in the Specialised Register section of information about Cochrane Kidney and Transplant.

See Appendix 1 for search terms and strategies used for this review.

Searching other resources

1. LILACS (Latin American and Caribbean Health Sciences) (from March 1980 to August 2022)
2. Reference lists of review articles, relevant studies and clinical practice guidelines
3. Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.

Data collection and analysis

Selection of studies

The search strategy described was used to obtain titles and abstracts of studies with potential relevance to the review. Titles and abstracts were screened independently by two authors who discarded studies that were not applicable; however, studies and reviews that could include relevant data or information

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on studies were retained initially. Two authors independently assessed retrieved abstracts and, if necessary, the full text of these studies to determine which satisfied the inclusion criteria.

Data extraction and management

Data extraction was carried out independently by two authors (AF, DB) using standard data extraction forms. Studies reported in non-English language journals were translated before assessment. Where more than one publication of one study existed, reports were grouped together, and the publication with the most complete data was used in the analyses. Where relevant outcomes were only published in earlier versions, these data were used. We resolved any discrepancies by discussion (AF, DB, AC).

Assessment of risk of bias in included studies

The following items were independently assessed using the risk of bias assessment tool (Higgins 2021) (see Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study?
  - Participants and personnel (performance bias)
  - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at risk of bias?

Measures of treatment effect

For normally distributed outcomes, we calculated summary estimates of treatment effects using the inverse variance method. For dichotomous outcomes (death, kidney recovery and adverse events), results were expressed as risk ratio (RR) with 95% confidence intervals (CI). Where continuous scales of measurement were used to assess the effects of treatment (length of stay, cost), the mean difference (MD) was used, or the standardised mean difference (SMD) if different scales were used. The results were interpreted taking into account the size of the effect (magnitude or importance) (see CKT 2017; EPOC 2013).

Unit of analysis issues

The unit of analysis was the participants of each arm (early or standard KRT initiation) that died, recovered of kidney function, the length of ICU and Hospital stay, or had adverse events.

Dealing with missing data

Any further information required from the original author was requested by written correspondence (e.g. emailing to the corresponding author), and any relevant information obtained in this manner was included in the review. Evaluation of important numerical data such as screened, randomised patients, as well as intention-to-treat, as-treated and per-protocol population, was carefully performed. Attrition rates, for example, drop-outs, losses to follow-up and withdrawals, were investigated. Issues of missing data and imputation methods (e.g. last-observation-carried-forward) were critically appraised (Higgins 2021).

Assessment of heterogeneity

Heterogeneity was analysed using a Chi^2 test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test (Higgins 2003). I^2 values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity.

Assessment of reporting biases

If possible, funnel plots were to be used to assess the potential existence of small study bias (Higgins 2021).

Data synthesis

Data were to be pooled using the random-effects model; however, the fixed-effect model was also used to ensure the robustness of the model chosen and susceptibility to outliers.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis was used to explore possible sources of heterogeneity (such as intervention, parameters to define early or standard initiation, participant and study quality). Heterogeneity among participants could relate to age, gender, fluid overload (< 10% and > 10% in body weight relative to baseline), and timing of KRT for AKI in homogenous subpopulations such as cardiac surgery or sepsis patients, effects of early initiation on the severity of illness. We used appropriate scores of illness severity, such as Pediatric Risk of Mortality (PRISM), Pediatric Index of Mortality (PIM), Acute Physiology and Chronic Health Evaluation (APACHE), Sequential Organ Failure Assessment (SOFA), and Cleveland Clinic ICU Acute Renal Failure (CCF). Adverse effects were tabulated and assessed using descriptive techniques. Where possible, the risk difference with 95% CI was calculated for each adverse effect, either compared with no treatment or another agent. In addition, where we identified important statistical or clinical heterogeneity, we performed meta-regression in order to explore the possible causes.

Sensitivity analysis

We performed sensitivity analyses to explore the influence of the following factors on effect size:

- Repeating the analysis, excluding unpublished studies
- Repeating the analysis taking account of the risk of bias
- Repeating the analysis, excluding any very long or large studies to establish how much they dominate the results
- Repeating the analysis excluding studies using the following filters: diagnostic criteria, the language of publication, source of funding (industry versus other), and country.

Summary of findings and assessment of the certainty of the evidence

We presented the main results of the review in 'Summary of findings' tables. These tables present key information concerning the quality of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data for the main outcomes. The 'Summary of findings' tables include an overall grading of the evidence related to each of the main outcomes using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach (GRADE 2008; CKT 2017). The GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity

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of specific interest. The quality of a body of evidence involves consideration of the within-study risk of bias (methodological quality), directness of evidence, heterogeneity, the precision of effect estimates and risk of publication bias (Schunemann 2021b). Summary of findings table 1 summarizes the main findings for the comparison "Early versus standard initiation of KRT for acute kidney injury". We presented the following outcomes.

- Death until day 30 post-randomisation
- Death after day 30 post-randomisation
- Death or non-recovery of kidney function at 90 days
- Kidney function recovery: number of patients free from KRT according to intention-to-treat analysis (all patients)
- Number of patients with hypotension, hypophosphataemia, cardiac-rhythm disorder and infections
- Length of ICU and hospital stay
- Subgroup analysis: death in patients who start KRT according to aetiology of AKI, recovery of kidney function by KRT modality.

RESULTS

Description of studies

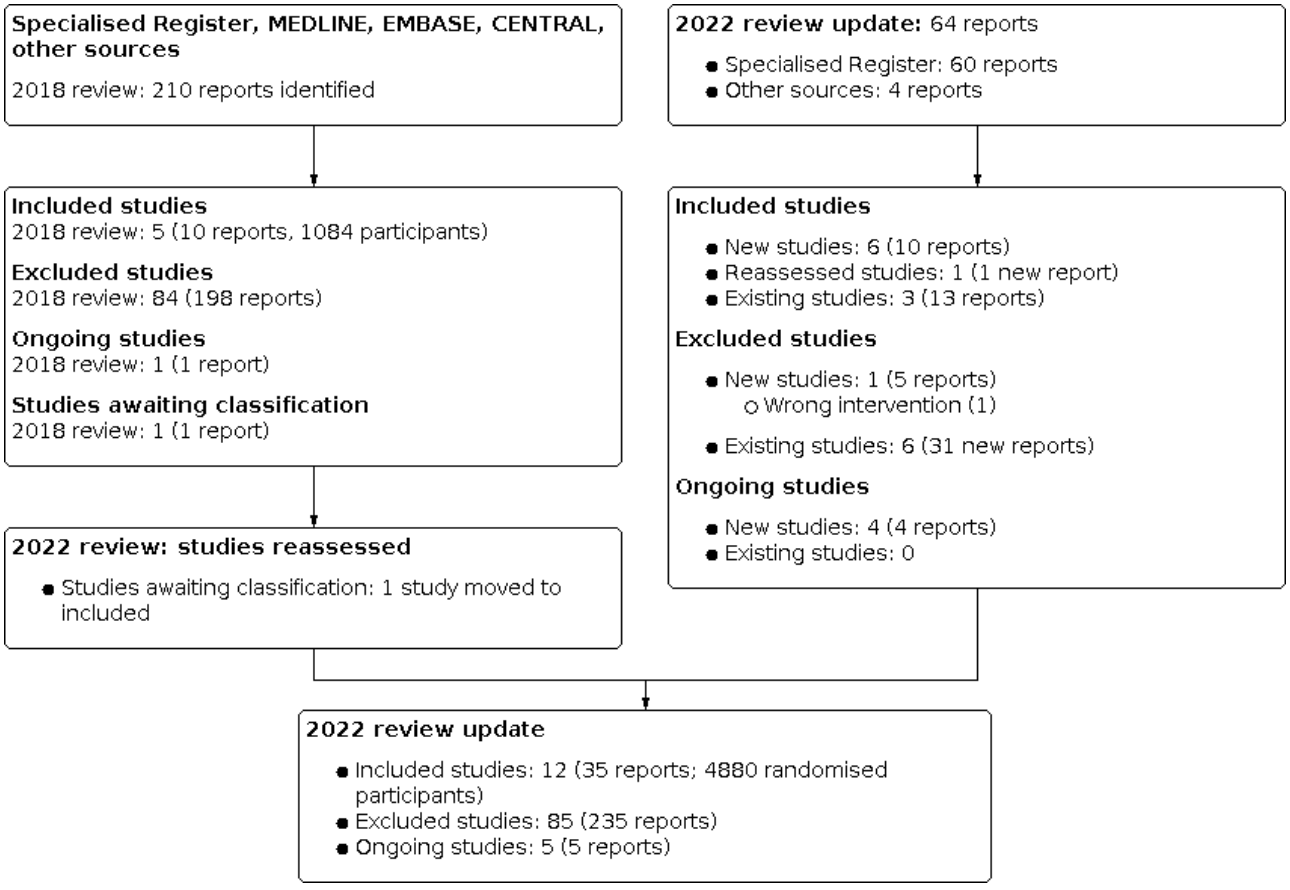
See Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies

Results of the search

Our 2018 review identified five studies (10 reports, 1084 participants) (AKIKI 2015; Bouman 2002; ELAIN 2016; STARRT-AKI 2019; Sugahara 2004), 84 excluded studies (198 reports), one ongoing study, and one study was awaiting classification.

For this 2022 review update, we searched Cochrane Kidney and Transplant's Specialised Register, LILACS and undertook additional handsearching and identified 64 new reports of 12 studies. Six new studies (10 reports) (EARLYRRT 2018; FST 2018; STARRT-AKI Pilot 2013; Tang 2016; Xia 2019; Yin 2018), and one study, previously awaiting classification (one new report) (IDEAL-ICU 2014), have been included in this update. Four new ongoing studies (four reports) were identified (Maiwall 2018; NCT02937935; CRTSAKI 2021; NCT03343340), and one new study (four reports) was excluded (AKIKI 2 2019). We also identified 44 new reports of existing included and excluded studies. See Figure 1.

Figure 1. Flow chart showing number of reports retrieved by database searching and the number of studies included in this review



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A total of 12 studies (35 reports, 4880 randomised participants) have been included, 85 studies excluded (235 reports), and there are five ongoing studies (five reports) in this 2022 update.

Included studies

Twelve studies (4880 participants) were included (AKIKI 2015; Bouman 2002; EARLYRRT 2018; ELAIN 2016; FST 2018; IDEAL-ICU 2014; STARRT-AKI Pilot 2013; STARRT-AKI 2019; Sugahara 2004; Tang 2016; Xia 2019; Yin 2018).

Study participants were all admitted to ICU. The mean age was between 62.8 and 69 years, and the proportion of males ranged from 49.6% to 70.4%. Surgery or cardio-surgery was the primary cause of AKI in three studies (Bouman 2002; ELAIN 2016; Sugahara 2004) and mixed (medical or surgical) in the other nine studies (AKIKI 2015; EARLYRRT 2018; FST 2018; IDEAL-ICU 2014; STARRT-AKI Pilot 2013; STARRT-AKI 2019; Tang 2016; Xia 2019; Yin 2018).

All studies were reported between 2002 and 2019. Six were single-centre studies (EARLYRRT 2018; ELAIN 2016; Sugahara 2004; Tang 2016; Xia 2019; Yin 2018), and six were multicentre (AKIKI 2015; Bouman 2002; FST 2018; IDEAL-ICU 2014; STARRT-AKI Pilot 2013; STARRT-AKI 2019).

Eight studies predominantly used CKRT (Bouman 2002; EARLYRRT 2018; ELAIN 2016; FST 2018; Sugahara 2004; Tang 2016; Xia 2019; Yin 2018), and four used combined therapies (intermittent and continuous) (AKIKI 2015; IDEAL-ICU 2014; STARRT-AKI Pilot 2013; STARRT-AKI 2019).

All the included studies assessed the effects of timing (early and standard) of KRT initiation on clinical outcomes of critical patients with AKI. In Bouman 2002, two of the three arms received the same timing of KRT initiation (early) but differed only in the intensities of continuous therapy. For the purpose of the analysis, we combined these two early treatment arms to create one early arm.

Sugahara 2004 did not report the treatment allocation of 8/36 participants that did not start the treatment. We assumed that they were evenly distributed among treatment arms (18 participants/arm). Similarly, we assumed that these eight participants had a favourable evolution (none of them died, and all of them recovered).

The included studies used a wide spectrum of definitions for early and standard initiation of KRT. Bouman 2002 and Sugahara 2004 defined early KRT initiation based on physiologic (urine output) and biochemical parameters (CrCl/SCr, respectively). Four studies defined early as starting KRT within 8 and 12 hours of fulfilling KDIGO stage 2 (ELAIN 2016; STARRT-AKI Pilot 2013),12 hours of fulfilling KDIGO stage 2-3 (STARRT-AKI 2019), 12 hours after the onset of failure stage of RIFLE (IDEAL-ICU 2014; Yin 2018), or within 6 hours of fulfilling KDIGO stage 3 (AKIKI 2015) and AKIN stage 2-3 (Tang 2016). The other three studies used any KDIGO stage and no response to the furosemide test as criteria of early KRT initiation (FST 2018) or an AKI biomarker (e.g. high urinary or serum NGAL) (EARLYRRT 2018; Xia 2019).

See Characteristics of included studies.

Excluded studies

We excluded 85 studies (235 records). Studies were excluded for the following reasons:

- Two reports in RENAL 2006 assessed timing; however, the study design was not randomised (retrospective nested cohort)
- Five studies did not mandate the presence of AKI (Durmaz 2003; HEROICS 2015; Han 2015; Koo 2006; Payen 2009) or ICU stay as inclusion criteria in the early initiation arm (Jamale 2013; Pursnani 1997)
- Two studies did not assess the outcomes of interest to this review (Cole 2002; Misset 1996)
- One study (AKIKI 2 2019) had no early intervention arm
- The remaining 72 studies did not assess the timing of KRT.

See Characteristics of excluded studies.

Risk of bias in included studies

Included studies were generally assessed to be at low or unclear risk of bias for most domains; two studies were assessed as high risk for incomplete outcome data (Sugahara 2004) and selective reporting bias (Tang 2016). Risk of bias assessments of the included studies are summarised in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

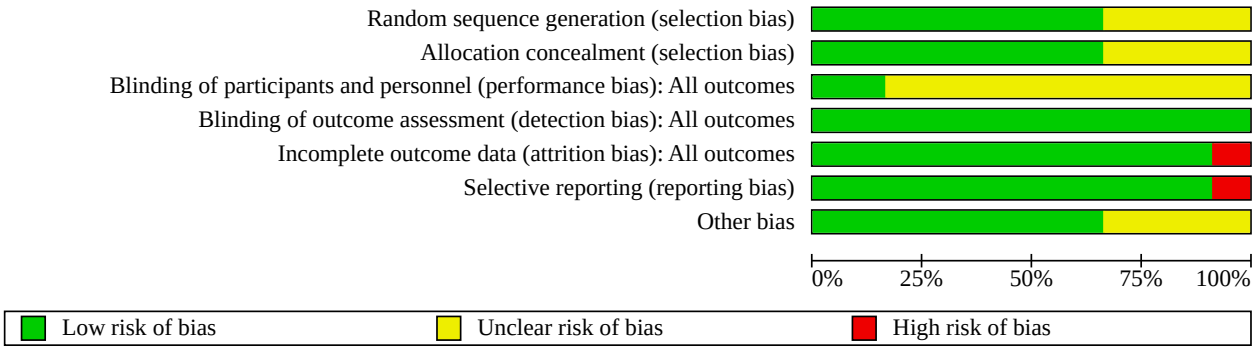

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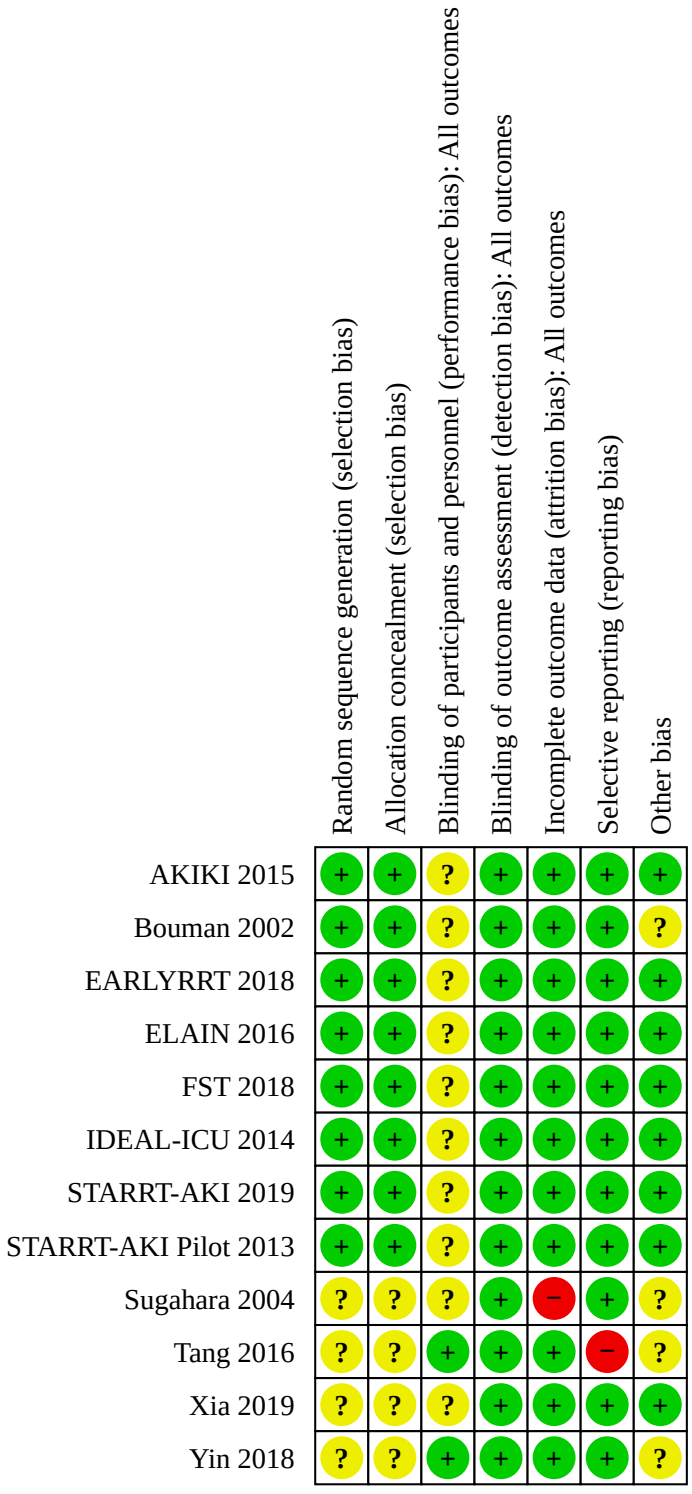
Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study



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Allocation

Two studies (Bouman 2002; FST 2018) did not provide detailed information on random sequence generation and allocation concealment processes. Authors were contacted, and we were informed that random sequence generation was appropriate (computer-generated), and sealed opaque envelopes were used for the allocation process. We did not receive an answer about the allocation process for four studies (Sugahara 2004; Tang 2016; Xia 2019; Yin 2018).

Seven studies (AKIKI 2015; Bouman 2002; ELAIN 2016; EARLYRRT 2018; IDEAL-ICU 2014; STARRT-AKI Pilot 2013; STARRT-AKI 2019) were assessed as being at low risk of selection bias due to appropriate random sequence generation (computer-generated) and for allocation concealment.

Random sequence generation and allocation concealment were considered unclear for four studies (Sugahara 2004; Tang 2016; Xia 2019; Yin 2018) as they did not provide sufficient information to enable judgment.

Blinding

Performance bias

Two studies were judged to be at low risk of performance bias (Tang 2016; Yin 2018), and the remaining nine studies were judged to be at unclear risk of performance bias (insufficient information to enable judgment).

Detection bias

All included studies were assessed at low risk of detection bias (outcome measurement was unlikely to be influenced by lack of blinding).

Incomplete outcome data

Sugahara 2004 was assessed at high risk of attrition (data from > 20% of randomised patients were not available for inclusion in the analysis). Intention-to-treat analysis was performed in the other 11 studies.

Selective reporting

The selective reporting bias was considered at high risk in Tang 2016 as not all of the expected outcomes were reported.

Other potential sources of bias

Eight studies were judged to be at low risk of bias. Four studies received pharmaceutical industry funding (ELAIN 2016; EARLYRRT 2018; STARRT-AKI Pilot 2013; STARRT-AKI 2019), which is a potential source of bias; however, the sponsors had no role in the design, data collection, analysis and results, review or approval of the manuscript so were judge to be at low risk of bias. The funding source was not available in the remaining four studies (Bouman 2002; Sugahara 2004; Tang 2016; Yin 2018), and these were judged to have unclear risk of bias.

Evaluation of publication bias

We constructed a funnel plot to investigate potential publication bias. Meta-analysis of death at day 30 was analysed. We found reasonable symmetry indicating a low risk of publication bias (Figure 4).

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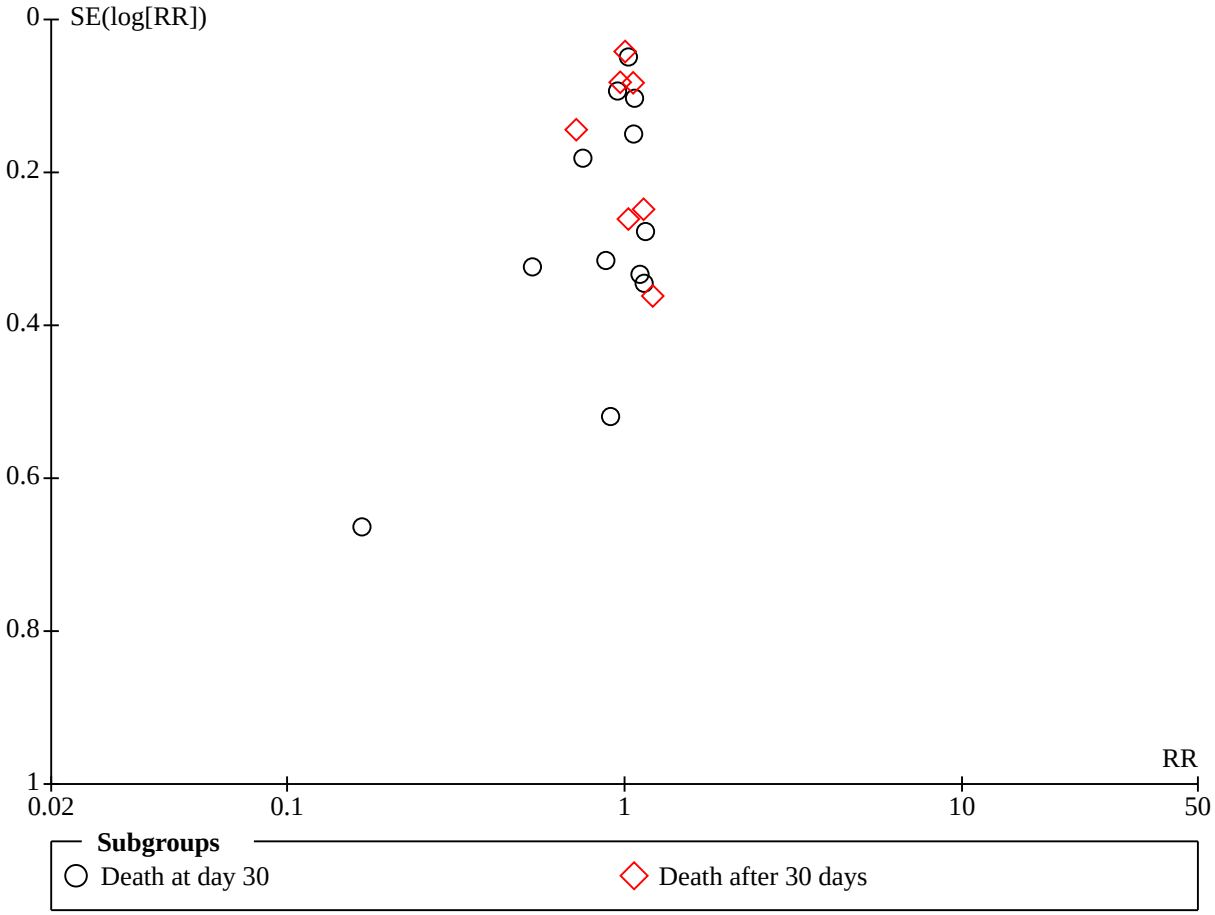
Figure 4. Funnel plot of comparison: 1 Early vs. late initiation, outcome: 1.1 Death.



Effects of interventions

See: **Summary of findings 1** Early versus standard initiation of kidney replacement therapy (KRT) in patients with acute kidney injury (AKI); **Summary of findings 2** Subgroup analyses: early versus standard initiation of kidney replacement therapy (KRT) in patients with acute kidney injury (AKI)

The effects of early KRT initiation versus standard for main results and the quality of the evidence are summarised in Summary of findings 1.

Death

All 12 studies assessed the effect of different timing of KRT initiation on death. These studies varied in reporting timing: 90 days (ELAIN 2016; IDEAL-ICU 2014; STARRT-AKI Pilot 2013; STARRT-AKI 2019); 60 days (AKIKI 2015); 28 days after randomisation (Bouman 2002; EARLYRRT 2018; FST 2018; Tang 2016; Xia 2019; Yin 2018); and 14 days after coronary bypass graft surgery (Sugahara 2004).

Compared to standard, early initiation of KRT may have little to no difference on the risk of death at day 30 (Analysis 1.1.1 (12 studies, 4826 participants): RR 0.97, 95% CI 0.87 to 1.09; I^2 = 29%; low certainty evidence). We assessed the certainty of evidence as low due to concerns about imprecision and heterogeneity. Early start probably made little or no difference to death after 30 days post-randomisation (Analysis 1.1.2 (7 studies, 4534 participants): RR 0.99, 95% CI 0.92 to 1.07; I^2 = 6%; moderate certainty evidence) in comparison with standard initiation. We assessed the certainty of evidence as moderate due to concerns about imprecision. The CI included both clinical benefits and harms.

Subgroup analysis and investigation of heterogeneity for death

There was evidence of moderate heterogeneity in the magnitude of the effect among the included studies that measured death at day 30 after randomisation. To explore heterogeneity among participants, we planned to perform pre-specified subgroup analyses according to the aetiology of AKI by criteria for the time of KRT initiation, modalities of KRT and severity of illness.

The effect of AKI aetiology was considered using two subgroups: patients with AKI secondary to surgical causes and patients with AKI related to non-surgical causes. Compared to standard, early KRT initiation probably made little or no difference to the risk of death in patients with non-surgical AKI (Analysis 2.1.1 (9 studies, 4461 participants): RR 1.01, 95% CI 0.94 to 1.09; I^2 = 0%; moderate certainty evidence) but may be reduced in surgical causes (Analysis 2.1.2 (3 studies, 365 participants): RR 0.65, 95% CI 0.31 to 1.36; I^2 = 70%; low certainty evidence).

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Despite mild heterogeneity between groups**,** the test for subgroup differences was not statistically significant. This could be explained by the studies being underpowered to detect differences due to the small sample size of the studies with the surgical-AKI group (Test for subgroup differences: $Chi^2 = 1.40$, df = 1; P = 0.24, $I^2 = 28.3\%$).

The effect of different criteria used to define the time of KRT initiation was assessed using three subgroups: patients starting KRT when fulfilling criteria to stage 2 of KDIGO classification, KDIGO 3 AKI RIFLE-F stage and AKIN stage 3 criteria, and patients initiating KRT according to other criteria (biomarkers, furosemide stress test). Compared to standard KRT, early strategy may make little or no difference to death in patients initiating KRT according to KDIGO 2 (Analysis 2.2.1 (3 studies, 3258 participants): RR 0.95; 95% CI 0.78 to 1.15; I^2 = 31%; low certainty evidence), KDIGO 3, AKI RIFLE-F stage, and AKIN stage 3 (Analysis 2.2.2 (4 studies, 1216 participants): RR 0.95; 95% CI 0.79 to 1.15; I^2 = 31%; low certainty evidence), or patients starting KRT according to other criteria (Analysis 2.2.3 (3 studies, 218 participants): RR 1.09, 95% CI 0.86 to 1.38; I^2 = 0%; moderate certainty evidence). There was no heterogeneity between groups (Test for subgroup differences: $Chi^2 = 0.92$, df = 2; P = 0.63, $I^2 = 0\%$).

The effect of KRT modalities was considered using two subgroups: patients with predominantly continuous kidney support and patients who received mixed modalities (continuous and intermittent). Compared to standard, early KRT initiation may make little or no difference to the risk of death in either the patients treated with CKRT (Analysis 2.3.1 (8 studies, 692 participants): RR 0.86, 95% CI 0.65 to 1.14; I^2= 48%; low certainty evidence) or patients treated with mixed modalities (Analysis 2.3.2 (4 studies, 4134 participants): RR 1.02, 95% CI 0.94 to 1.10; I^2 = 0%; moderate certainty evidence). There was no significant heterogeneity between groups (Test for subgroup differences: Chi^2 = 1.23; df = 1; P = 0.27, $I^2 = 18.8\%$).

The effect of the severity of illness at baseline was assessed using two subgroups: patients with high and low SOFA scores (> 12 and ≤ 12). Compared to standard, early KRT initiation may make little or no difference to the risk of death in patients with either a SOFA score > 12 (Analysis 2.4.1 (3 studies, 819 participants): RR 0.95; 95% CI 0.75 to 1.20; I^2= 31%; low certainty evidence) or those with a SOFA score ≤ 12 (Analysis 2.4.2 (6 studies, 3870 participants): RR 1.02; 95% CI 0.94 to 1.10; I^2 = 0%; moderate certainty evidence). There was no heterogeneity between groups (test for subgroup differences: Chi^2 = 0.35; df = 1; P = 0.55; $I^2 = 0\%$).

See Summary of findings 2.

Sensitivity analysis

The sensitivity analysis was performed excluding studies by the risk of bias and size of the study. When taking risk of bias into account, we observed that Sugahara 2004 contributed to heterogeneity, and, when excluded, heterogeneity was not significant (P = 0.62; $I^2 = 0\%$). The reason for exclusion was incomplete outcome data (attrition bias), but the overall estimation of effect did not change, and the direction of effects remained constant. We found no changes in heterogeneity when the study with the larger sample size was excluded.

Death or non-recovery of kidney function at 90 days

This composite outcome was available for six studies (AKIKI 2015; Bouman 2002; ELAIN 2016; STARRT-AKI 2019; STARRT-AKI Pilot 2013; Sugahara 2004). Compared with standard, early initiation may make little or no difference to the risk of death or non-recovery of kidney function at 90 days (Analysis 1.2 (6 studies, 4011 participants): RR 0.91, 95% CI 0.74 to 1.11; I^2 = 66%; low certainty evidence). We assessed the certainty of evidence as low due to concerns about imprecision and heterogeneity. However, the CIs included clinically important benefits and harms.

Subgroup analysis and investigation of heterogeneity for death or non-recovery of kidney function at 90 days

Compared to standard, early KRT initiation probably made little or no difference to the risk of death or non-recovery of kidney function at 90 days with either non-surgical AKI (Analysis 3.1.1 (3 studies, 3646 participants): RR 1.04, 95% CI 0.97 to 1.11; I^2 = 0%; moderate certainty evidence), or surgical causes (Analysis 3.1.2 (3 studies, 365 participants): RR 0.66, 95% CI 0.33 to 1.33; I^2 = 70%; low certainty evidence). The test for subgroup differences was not significant (Chi^2 = 1.60; df = 1; P = 0.21; $I^2 = 37.5\%$).

Compared to standard KRT, the early strategy may make little or no difference to death or non-recovery of kidney function at 90 days in patients initiating KRT according to KDIGO 2 (Analysis 3.2.1 (1 study, 619 participants): RR 0.95; 95% CI 0.79 to 1.11; low certainty evidence), KDIGO 3, AKI RIFLE-F stage, and AKIN stage 3 (Analysis 3.2.2 (3 studies, 3258 participants): RR 0.91; 95% CI 0.70 to 1.19; I^2 = 70%; low certainty evidence), or patients starting KRT according to other criteria (Analysis 3.2.3 (2 studies, 134 participants): RR 0.47, 95% CI 0.07 to 3.21; I^2 = 0%; low certainty evidence). There was no heterogeneity between groups (test for subgroup differences: Chi^2 = 0.56; df = 2; P = 0.76; $I^2 = 0\%$).

Compared to standard, early KRT initiation may make little or no difference to the risk of death or non-recovery of kidney function at 90 days in either patients treated with CKRT (Analysis 3.3.1 (3 studies, 365 participants): RR 0.66, 95% CI 0.33 to 1.33; I^2= 70%; low certainty evidence) or patients treated with mixed modalities (Analysis 3.3.2 (3 studies, 3646 participants): RR 1.04, 95% CI 0.97 to 1.11; I^2 = 0%; moderate certainty evidence). The test for subgroup differences was not significant (Chi^2 = 1.60; df = 1; P = 0.21; I^2 = 37.5%).

Compared to standard, early KRT initiation may reduce the risk of death or non-recovery of kidney function at 90 days in patients with a SOFA score > 12 (Analysis 3.4.1 (2 studies, 331 participants): RR 0.77; 95% CI 0.62 to 0.97; I^2= 0%; low certainty evidence), but not in those with a SOFA score ≤ 12 (Analysis 2.4.2 (3 studies, 3652 participants): RR 1.04; 95% CI 0.97 to 1.12; I^2 = 0%; low certainty evidence). The test for subgroup differences was significant (Chi^2 = 6.07; df = 1; P = 0.01; $I^2 = 83.5\%$).

Sensitivity analysis

The sensitivity analysis was performed, excluding studies by the risk of bias and studies with large sample sizes. When the analysis was developed taking risk of bias into account, we observed that Sugahara 2004 contributed to heterogeneity, and, when excluded, heterogeneity was not significant (P = 0.12; $I^2 = 46\%$). The reason for exclusion was study limitation (attrition bias), but the overall estimation of effect did not change, and the direction of

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effects remained constant. We found no changes in heterogeneity when the studies with larger sample sizes were excluded.

Recovery of kidney function

Ten studies reported information on recovery of kidney function (in all patients and among patients' survivors). Studies varied in reporting of kidney recovery timing: at 90 days after randomisation (AKIKI 2015; ELAIN 2016; EARLYRRT 2018; IDEAL-ICU 2014; STARRT-AKI Pilot 2013; STARRT-AKI 2019), 28 days or at hospital discharge (Bouman 2002; Xia 2019; Yin 2018), or 14 days after coronary bypass graft surgery (Sugahara 2004).

Compared to standard, early KRT initiation may make little or no difference to the number of patients free from KRT according to intention-to-treat analysis (Analysis 1.3.1 (10 studies, 4717 participants): RR 1.07, 95% CI 0.94 to 1.22; I^2=55%; low certainty evidence). We assessed the certainty of evidence as low due to concerns about imprecision and heterogeneity.

Among survivors free from KRT according to intention to treat analysis, after day 30, early initiation of KRT may make little or no difference to the recovery of kidney function compared to standard (Analysis 1.3.2 (10 studies, 2510 participants): RR 1.02, 95% CI 0.97 to 1.07; I^2 = 69%; low certainty evidence). We assessed the certainty of evidence as low due to concerns about indirectness and heterogeneity. The CIs of both outcomes included clinical benefits and harms.

Subgroup analysis and investigation of heterogeneity recovery of kidney function

There was evidence of heterogeneity in the magnitude of the effect among the included studies that measured recovery of kidney function in all patients at different times after randomisation. To explore heterogeneity among participants, we planned to perform pre-specified subgroup analyses. Only data for AKI aetiology, parameters of early initiation and modalities were available.

Compared to standard, early KRT initiation may make little or no difference to the recovery of kidney function in patients with AKI related to either surgical causes (Analysis 4.1.1 (3 studies, 365 participants): RR 1.36, 95% CI 0.78 to 2.38; I^2 = 78%; low certainty evidence) or non-surgical AKI (Analysis 4.1.2 (7 studies, 4095 participants): RR 1.00, 95% CI 0.91 to 1.11; I^2 = 27%; low certainty evidence). The test for subgroup differences was not significant (Chi^2 = 1.10; df = 1; P = 0.29; I^2 = 9.4%).

Compared to standard, early initiation KRT may make little to no difference to the recovery of kidney function in patients initiating KRT according to KDIGO 2 criteria (Analysis 4.2.1 (3 studies, 3258 participants): RR 1.08, 95% CI 0.86 to 1.36; I^2 = 70%; low certainty evidence), or KDIGO3, AKI RIFLE-F stage and AKIN 3 criteria (Analysis 4.2.2 (2 studies, 1107 participants): RR 1.00, 95% CI 0.88 to 1.13; I^2 = 0%; low certainty evidence), while it may increase kidney recovery according to other criteria (Analysis 4.2.3 (3 studies, 218 participants): RR 1.55; 95% CI 0.95 to 2.53; I^2 = 26%; low certainty evidence). The test for subgroup differences was not significant, and this could be explained by the small sample size and the small number the studies in each subgroup (test for subgroup differences: Chi^2 = 3,07; df = 2; P = 0.22; I^2 = 34.9%).

Compared to standard, early KRT initiation may make little or no difference to the recovery of kidney function in patients treated with CKRT (Analysis 4.3.1 (6 studies, 583 participants): RR 1.42, 95% CI 0.99 to 2.03; I^2 = 60%; moderate certainty evidence), and in patients treated with mixed modalities (Analysis 4.3.2 (4 studies, 4134 participants): RR 0.96, 95% CI 0.91 to 1.02; I^2 = 0%; moderate certainty evidence). There was significant heterogeneity between the groups, and the test for subgroup differences was significant (Chi^2 = 4.27; df =1; P = 0.04; I^2 = 76.6%). This heterogeneity could be explained by different KRT modalities.

See Summary of findings 2.

Sensitivity analysis

The sensitivity analysis was performed, excluding studies at high risk of bias and studies with large sample sizes. When the analysis was developed taking risk of bias into account, we observed that Sugahara 2004 contributed to heterogeneity, and when excluded, heterogeneity was not significant (P = 0.08; I^2 = 44%). The reason for exclusion was study limitation (attrition bias); however, the overall estimation of effect did not change, and the direction of effects remained constant. We found no changes in heterogeneity when the study with a larger sample size was excluded.

Adverse events

The effects of the timing of KRT initiation on adverse events were reported in seven studies (AKIKI 2015; Bouman 2002; ELAIN 2016; IDEAL-ICU 2014; FST 2018; STARRT-AKI Pilot 2013; STARRT-AKI 2019).

It is uncertain whether early KRT initiation increases or reduces the number of patients who experienced any adverse events compared to standard (Analysis 1.4.1 (5 studies, 3983 participants): RR 1.23, 95% CI 0.90 to 1.68; I^2 = 91%; very low certainty evidence). We assessed the certainty of evidence to be very low due to concerns about imprecision and very serious inconsistency.

Early KRT initiation increased the risk of hypophosphataemia (Analysis 1.4.2 (1 study, 2927 participants): RR 1.80, 95% CI 1.33 to 2.44), hypotension (Analysis 1.4.3 (5 studies, 3864 participants): RR 1.54, 95% CI 1.29 to 1.85; I^2 = 0%), cardiac-rhythm disorder (Analysis 1.4.4 (6 studies, 4483 participants): RR 1.35, 95% CI 1.04 to 1.75; I^2 = 16%), and infection (Analysis 1.4.5 (5 studies, 4252 participants): RR 1.33, 95% CI 1.00 to 1.77; I^2 = 0%); with high certainty evidence.

Early start probably reduced the risk of bleeding (Analysis 1.4.6 (6 studies, 4358 participants): RR 0.91, 95% CI 0.73 to 1.18; I^2 = 4%; moderate certainty evidence). We assessed the certainty of evidence as moderate due to concerns about imprecision. However, it is uncertain whether early start of KRT increases or decreases the risk of thrombocytopenia (Analysis 1.4.7 (1 study, 106 participants): RR 1.03, 95% CI 0.20 to 5.35; very low certainty evidence) compared with standard initiation. We assessed the certainty of evidence as very low due to concerns about very serious imprecision and study limitation (small sample size).

Sensitivity analysis

The sensitivity analysis was performed, excluding studies at high risk of bias and studies with large sample sizes. When the analysis was developed taking the study with a larger sample size into account, we found that STARRT-AKI 2019 contributed to heterogeneity, and when was excluded, heterogeneity decreased but remained significant (P = 0.03; I^2 = 66%). The reason for exclusion was a large study; however, the overall estimation of

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effect did not change, and the direction of effects remained constant. We found no changes in heterogeneity when the study at high risk of bias was excluded.

Length of stay

Seven studies assessed the effect of timing on length of stay (AKIKI 2015; Bouman 2002; ELAIN 2016; FST 2018; IDEAL-ICU 2014; STARRT-AKI Pilot 2013; STARRT-AKI 2019).

Early KRT initiation probably reduces the number of days in ICU (Analysis 1.5.1 (5 studies, 4240 participants): MD -1.01 days, 95% CI -1.60 to -0.42; I^2 = 0%; moderate certainty evidence) compared to standard. We assessed the certainty of evidence as moderate due to concerns about indirectness.

Likewise, early KRT probably reduces the number of days in hospital compared with standard KRT initiation (Analysis 1.5.2 (7 studies,4589 participants): MD -2.45 days, 95% CI -4.75 to -0.14; I^2 = 10%; moderate certainty evidence). We assessed the certainty of evidence as moderate due to concerns about indirectness.

Cost

This outcome was not reported by any of the included studies. We did not identify high-quality non-RCTs reporting safety and cost outcomes.

Meta-regression

Considering that we found statistical and clinical heterogeneity on main outcomes, we performed non-prespecified meta-regression using STATA 14.1 to explore the effect of co-variables for which we had data.

1. **Type of participants** (patients with AKI related to non-surgical causes or patients with AKI related to surgical causes)
2. **Fluid overload** (FO) after randomisation, based on the three categories (FO ≤ 3 L, FO = 3 to < 6 L and FO ≥ 6 L)
3. **Absolute difference** in fluid overload after randomisation between standard group minus interventions group
4. **KRT modality** (continuous and intermittent + continuous)
5. **Hypotension**: difference between the percentage of patients with hypotension in the early group minus the standard group.

We performed meta-regression on the primary and secondary outcomes with results of six to nine studies: death at day 30, kidney recovery function in all patients, and hospital length of stay. We did not find significant results explaining sources of heterogeneity using this analysis. None of the explanatory variables analysed influenced the size of the intervention or affected the outcomes evaluated. Details on the definitions of variables, data set, and outcomes measures are available in Appendix 3

In order to show some aspects of the heterogeneous results, we present crude results of the investigated outcomes for the six and nine included studies. The files of the table were ordered from top to bottom by type of patient, fluid overload, the difference in the amount of fluid overload after randomisation, hypotension, and KRT modality between groups (See Appendix 4; Appendix 5; Appendix 6).

DISCUSSION

Summary of main results

Our systematic review and subsequent meta-analysis examined the effect of different timing of initiation of KRT on death, kidney recovery function, length of stay, and adverse events among 4880 randomised critically ill patients with AKI. Most of the included studies were assessed as having a low or unclear risk of bias for all domains. Two studies were assessed as having a high risk bias, one for incomplete outcome data (attrition bias) and the other for selective reporting (reporting bias).

Within the time of KRT initiation assessed, earlier start may have no beneficial effect on death or recovery of kidney function (in all patients) compared to standard strategy.

Within the time of KRT initiation assessed, earlier start may have little to no difference on death at day 30**.** The overall estimated effects on risk of death showed clinically small benefits (decreased death by 3%), but the CIs were sufficiently wide to include benefits and harm (imprecision), with a low level of heterogeneity (I^2 = 29%; inconsistency). The 3% relative risk reduction (RRR) in death at day 30 in the early KRT group is related to a reduction in absolute risk observed in only 12 of 1000 patients (50 less or 35 more than those treated with late KRT), thus assuming little to no effect on death.

Early strategy probably makes little to no difference on death after day 30, with imprecision and without inconsistency (I^2 = 6%).

Early strategy may make little or no difference to the risk of death or non-recovery of kidney function at day 90. The overall estimated effects on risk of death showed clinical benefits (decreased death by 9%), but the CIs were sufficiently wide to include benefits and harm (imprecision), with a moderate level of heterogeneity (I^2 = 66%; inconsistency). However, when we removed Sugahara 2004, the I^2 is reduced to 46%, and the imprecision was also reduced. There are no significant differences between the groups (subgroup test P = 0.12, I^2 = 43%). The RR went from 0.91 (95% CI 0.74 to 1.11) to 0.96 (95% CI 0.83 to 1.10), which is compatible with little to no difference in death or non-recovery kidney function at day 90. This study was assessed as having a high risk of bias by incomplete outcome data (attrition bias) (See Sensitivity analysis and Overall completeness and applicability of evidence).

Early start may make little or no difference to the number of patients who recovered kidney function. CIs included damage (imprecision), with a moderate level of heterogeneity (I^2 = 55%; inconsistency). There was little to no difference in kidney recovery among survivors between interventions. However, reporting kidney recovery among survivors alone does not preserve the previously achieved randomisation. Therefore, the interpretation of this result may be misleading, given death is a competing endpoint for recovery of kidney function in patients with a high short-term risk of death (indirectness). However, when we removed three studies (EARLYRRT 2018; Sugahara 2004; Xia 2019), the I^2 was reduced to 25%. The RR went from 1.07 (95% CI 0.94 to 1.22) to RR 1.00 (95% CI 0.92 to 1.09), which is compatible with little to no difference in the recovery of kidney function. These studies were sources of heterogeneity probably due to selection bias (Sugahara 2004; Xia 2019), attrition bias (Sugahara 2004) and no blinding (EARLYRRT 2018; Sugahara 2004; Xia 2019), thus limiting the internal validity. Xia 2019 and EARLYRRT 2018 used AKI-

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biomarker (high level of urinary or serum NGAL) as criteria for early KRT initiation.

It is uncertain whether early KRT initiation increases or reduces the number of patients who experienced any adverse events compared to standard, with a substantial level of heterogeneity (I^2 = 91%; inconsistency). Nevertheless, the early strategy did increase the risk of hypophosphataemia, hypotension, cardiac rhythm disorder and infections, although it had uncertain effects on thrombocytopenia and the risk of bleeding when compared to standard initiation.

Early start probably reduces the length of ICU and hospital stay (number of days). The magnitude of the possible benefit was clinically relevant (-1.01 days to -2.45 days, respectively). These results should be interpreted with caution owing to the indirectness observed (in this population, death is a competing endpoint for the length of stay).

With a focus on the effect size of the central estimation (magnitude or importance), we observed that early initiation may make little to no difference to death, may improve the recovery of kidney function, probably reduces the length of ICU and hospital stay, while it increased the risk of adverse events. However, all results (except any adverse events and length of stay) were imprecise because the CIs crossed both the important effect threshold and the no difference threshold.

An important limitation of this systematic review was the low to moderate heterogeneity found in the main results, as death at day 30 (I^2 = 29%), death or non-recovery of kidney function at 90 days (I^2 = 66%), and on recovery of kidney function in all patients (I^2 = 55%). There was no heterogeneity identified for the length of stay, and adverse events (hypophosphataemia, hypotension, cardiac rhythm disorder and infections), except for the number of patients with any adverse event (I^2 = 91%).

We explored this heterogeneity by prespecified subgroup analyses: aetiology of AKI, according to criteria used to define the timing of KRT initiation, modalities of KRT, and the severity of illness at baseline. The subgroup modality of KRT initiation was identified as a source of heterogeneity in the size of the effect observed in the recovery of kidney function (test for subgroup differences: Chi^2 = 4.27; P = 0.04; I^2 = 76.6%). These results should be interpreted with caution as only five small studies contributed to these data. Notably, several studies reported that there were more hypotension events with intermittent haemodialysis, which was more likely to result in haemodynamic instability than CKRT, with a lower likelihood of kidney recovery after AKI.

In the subgroup of aetiology of AKI, we observed a reduction in death (35%) in patients with surgery-acquired compared to those patients with non-surgery-acquired AKI (increased risk 1%). Despite some heterogeneity (I^2 = 28.3%) between groups, the test for subgroup difference was not statistically significant. This could be explained by the studies being underpowered to detect differences due to the small sample size of the studies with the surgical-AKI group. However, if we remove Sugahara 2004, the I^2 is reduced to 13%, and the imprecision is also reduced. The RR goes from 0.65 (95% CI 0.31 to 1.36) to 0.84 (95% CI 0.59 to 1.20). The effect size is lower but still clinically relevant. This study was assessed as having a high risk of bias by incomplete outcome data (attrition bias) (See Overall completeness and applicability of evidence).

In the subgroup of KRT modalities reduction in death (14%) was observed in patients with CKRT compared to those patients with mixed KRT modality (increased risk 2%). Without heterogeneity (I^2 = 0%) between groups, the test for subgroup difference was not statistically significant. However, when we removed Sugahara 2004, the I^2 is reduced from 48% to 7%, and the imprecision was also reduced. The RR goes from 0.86 (95% CI 0.65 to 1.14) to 0.93 (95% CI 0.77 to 1.13) (See Overall completeness and applicability of evidence).

In the subgroup of aetiology of AKI, we observed an increase in kidney recovery rate (36%) in patients with surgery-acquired compared to those patients with non-surgery-acquired AKI. Without (I^2 = 9.4%) between groups, the test for subgroup difference was not statistically significant. This could be explained by the underpowered to detect differences due to the small sample size of the studies with the surgical-AKI group. However, if we remove Sugahara 2004, the I^2 is reduced to 0%, and the imprecision was also reduced. The RR goes from 1.36 (95% CI 0.78 to 2.38) to 1.12 (95% CI 0.72 to 1.74). The effect size is lower but still clinically relevant. This study was assessed as having a high risk of bias by incomplete outcome data (attrition bias) (See Overall completeness and applicability of evidence).

For the death or non-recovery of kidney function at 90 days, the subgroups aetiology (surgical and non-surgical), initiation criteria KDIGO 2, KDIGO 3, AKI RIFLE-F stage, and AKIN stage 3, or other criteria) and modality (CKRT or mixed KRT) made little or no difference to this outcome. Early initiation may reduce the risk of death or non-recovery of kidney function at 90 days in patients with a SOFA score > 12 but not in those with a SOFA score ≤ 12.

RCTs focusing on the timing of KRT initiation for paediatric AKI patients were not available.

Overall completeness and applicability of evidence

Although the analyses included data obtained from a comprehensive and rigorous search, we identified gaps in several areas. The majority of participants in the included studies were adults, limiting the applicability of our finding to children. In general, the incidence of AKI secondary to sepsis in ICU is high; however, in three studies, it was observed that the majority of patients had post-surgical AKI, and relatively few had sepsis or pre-existing chronic kidney disease (CKD), limiting the applicability of our results to general ICU population.

Six studies were single-centre, and all were unblinded, limiting the external and internal validity of the results, respectively.

Data on the number of patients with any adverse events were limited and only provided by five of the 12 studies in our review.

Few studies reported data for KRT dosage and volume overload; we are aware that it is an important issue to consider in relation to death in critically ill patients with AKI.

Most of the studies did not report data on death in patients with pre-existing CKD.

There were large variations in the definition of the timing of KRT initiation among included studies. Heterogeneous indicators such as different serum urea or SCr levels, urine output, time from randomisation and time to fulfil KDIGO AKI stage, biochemical

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markers and furosemide test are widely used to measure the timing of KRT; however, this approach provides an incomplete assessment of optimal timing of KRT initiation in this population and limits the applicability of our results.

It is important to highlight the absence of data related to the characteristics and evolution of patients randomised to the standard or late arm who did not receive dialysis treatment. These data would allow us to develop a propensity-based analysis of patients in the accelerated group and among those who did not receive KRT in the standard/delayed strategy in order to define where these patients could have had a better outcome.

We were unable to address all of the objectives of this review due to the lack of data in the included studies. Also, we did not have individual patient data for the different subgroups of the modality of KRT and aetiology of AKI, being a limitation of our review

The RCTs included as well as recent research by Gaudry 2020, provided new knowledge and tools, such as the use of furosemide stress test or emerging biomarkers of persistent severe AKI and clinical judgment, that will help us define the optimal KRT initiation time in order to recognize when early KRT initiation may be essential for better outcomes or unnecessary due to potential harms for AKI-patients in ICU.

We included only RCTs with the purpose of reducing bias.

Quality of the evidence

We conducted this review according to the process described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021). Our review was based on evidence from 12 RCTs (4880 randomised participants) that compared different timing of KRT initiation in critically ill patients with AKI. The certainty evidence for our main outcomes was drawn from studies assessed at low risk of bias for random sequence generation and allocation concealment processes, incomplete outcomes data, intention to treat analysis, selective outcomes reporting, performance and detection bias and other sources of bias; as well as unclear risk for detection bias. Two studies were at high risk of bias by incomplete outcome data (attrition bias) and selective reporting (reporting bias). Three small studies had an unclear risk of selection bias.

Data comparing the effect of early KRT initiation against standard initiation on death at day 30 or after were obtained from 12 and seven well-conducted RCTs, respectively, but we downgraded the certainty of evidence to low, mainly due to inconsistency (I^2 = 29%) and imprecision (CIs included a range of plausible value with clinically important benefits, but also harm), and rated it as moderate by imprecision for death after 30 days. Similarly, we downgraded the certainty of evidence to low for recovery of kidney function in all patients due to imprecision and inconsistency (I^2 = 55%) and rated as low data obtained for recovery of kidney function among survivors by inconsistency (I^2 = 69%) and indirectness (the recovery of kidney function in this high-risk group is affected when the risk of death is taken into account).

Data used to assess the impact of early versus standard initiation of KRT on adverse events were obtained from eight well-conducted RCTs, providing treatment effects with clinically important harms for hypophosphataemia, hypotension, cardiac-rhythm disorder and infections. We rated this as high-certainty evidence. Six studies reported the number of patients with bleeding; and were rated as moderate by imprecision. One study provided data on the number of patients with thrombocytopenia; we downgraded the certainty of evidence to very low due to serious imprecision and study limitation (one study with a small sample size). In the same way, we downgraded the certainty of evidence as very low owing to imprecision and substantial inconsistency (I^2= 91%) observed in the number of patients with some kind of adverse event (data provided by five RCTs).

Length of ICU and hospital stay was reported by five and seven RCTs, respectively; we downgraded the certainty of evidence to moderate due to indirectness, as death is a competing endpoint for the length of stay in this population.

Potential biases in the review process

While this review was conducted according to rigorous methods developed by the Cochrane Collaboration, some bias may be present in the review process. We searched for all relevant studies using sensitive and validated strategies in major medical databases and grey literature sources. However, it is possible that some studies (such as unpublished data and studies with negative or no effects) were not identified. An analysis of evidence to assess the risk of publication bias was not possible for all outcomes due to the number of studies available in each meta-analysis (Figure 4).

Several subgroup analyses were planned to explore potential sources of heterogeneity in our review; however, a lack of data prevented us from performing these analyses.

Agreements and disagreements with other studies or reviews

Our systematic review, in keeping with previous meta-analyses on timing in KRT (Gaudry 2020; Li 2021; Naorungroj 2021; Pan 2021), found that earlier KRT initiation may have no beneficial effect on death in critically ill patients with AKI compared with later strategy. These results were not consistent with two other systematic reviews that included randomised and observational studies (Seabra 2008; Wierstra 2016) and other meta-analyses based only on RCTs (Mavrakanas 2017; Wang 2017; Xu 2017)

The hypothesis that critical AKI patients, especially those with acidaemia, fluid overload, or systemic inflammation, could benefit from early KRT was proposed by several researchers. Our review has found that early strategy may have little to no difference on death at day 30. This result is consistent with five multicentre RCTs (AKIKI 2015; Bouman 2002; IDEAL-ICU 2014; STARRT-AKI Pilot 2013; STARRT-AKI 2019) but does not agree with those reported in three individual RCTs (ELAIN 2016; Tang 2016; Sugahara 2004)

It is important to note that differences in death between AKIKI 2015 and ELAIN 2016 were observed (41.6% versus 30.4% at day 30, respectively). These differences may be due to several factors, which include: different severity levels and aetiology of AKI, e.g. prevalence of patients with AKI related to surgical cause in the ELAIN 2016 or septic AKI-patients was more frequent in AKIKI 2015; both aetiologies have different pathophysiology and prognosis), and variable criteria for defining early KRT initiation (KDIGO AKI stage 3 for AKIKI 2015 and KDIGO AKI stage 2 for ELAIN 2016).

Other timing criteria were observed: serum and urinary biomarkers (EARLYRRT 2018; Xia 2019), or furosemide test (FST 2018), and

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the equipoise judgment of clinicians for inclusion in the standard arm (STARRT-AKI Pilot 2013; STARRT-AKI 2019) (See Overall completeness and applicability of evidence).

There has been increased interest in the recovery of kidney function. Indeed, lack of recovery of kidney function implies the need for long-term dialysis associated with low quality of life and high health costs. Our review has found that early strategy may have a slightly beneficial effect on the recovery of kidney function in all patients. This finding is consistent with two individual RCTs (ELAIN 2016; Sugahara 2004) (with high kidney recovery rate), and does not agree with the other three multicentre RCTs (AKIKI 2015; Bouman 2002; STARRT-AKI Pilot 2013). Differences in the recovery of kidney function between studies may be due to the same factors mentioned above. However, in patients with a high short-term death risk, the interpretation of this result may be misleading, given that death is a competing endpoint for recovery of kidney function (Palevsky 2005).

Patients with AKI experience longer ICU and hospital stays. In our review, the earlier strategy probably reduce ICU and hospital length of stay; this result is consistent with individual RCTs and meta-analyses (ELAIN 2016; STARRT-AKI Pilot 2013; Naorungroj 2021) and does not agree with other RCT reports (AKIKI 2015; IDEAL-ICU 2014) and meta-analyses (Gaudry 2020; Li 2021). However, the length of stay in this high-risk population may be affected when death is taken into account.

There was an increased risk in the number of patients who had specific adverse events with early initiation of KRT compared with standard. Our results were consistent with other RCTs (Bouman 2002; STARRT-AKI 2019) and meta-analyses (Li 2021; Naorungroj 2021).

Our review has an important limitation due to the heterogeneity observed in the main outcomes. Only in kidney recovery did we find an association between the estimated effect and KRT modality in agreement with a recent meta-analysis (Pan 2021). We were unable to address all of the pre-specified subgroup analyses of this review due to the lack of data in the included studies.

Our review includes studies of different countries (Europe, North America and Asia) which increase the applicability of these results.

Previous reviews explored the effect of time to KRT initiation in patients with AKI; however, these reviews included studies that we excluded from our review due to the following factors: different inclusion criteria applied, e.g. hospitalised patients were not in an ICU setting (Pursnani 1997) or did not require AKI for enrolment in the early arm (Durmaz 2003; HEROICS 2015; Jamale 2013; Koo 2006) and differences in the methodological studies design (cohort studies). Although the abundance of cohort studies provided more power (increases the sample size) to find significant clinical differences between both treatments, these studies have important limitations: patients between intervention groups were different (e.g. patients assigned to late arm treatment might have died before initiating the therapy, while others who lived enough to be assigned to the late group might have been less sick or with a high likelihood of recovering kidney function without KRT). A relevant point worth considering is that patients do not have the same opportunity to receive early or standard treatment (allocation or selection bias). Consequently, to minimise the risk of bias in our review, we included only RCTs for our main outcomes.

AUTHORS' CONCLUSIONS

Implications for practice

Earlier KRT may have little to no difference to death at day 30 or recovery of kidney function, although in both results, the CIs included clinical benefits and harm.

Earlier KRT initiation probably reduces ICU and hospital length of stay. Nevertheless, an increased risk of adverse events was observed when compared to a later KRT strategy.

The absence of high-quality evidence of efficacy and the possibility of increased adverse events do not support the routine use of early KRT in critically ill patients with AKI.

These results do not minimise the importance of the timing of KRT in this population but rather reinforce the need to better understand in what cases earlier initiation translates into improved patient outcomes. Minimal standards for the initiation of KRT appear to have been identified in different guidelines (KDIGO 2012; NICE 2013; Vinsonneau 2015); however, these approaches provide an incomplete assessment of the optimal timing of KRT.

Recent RCTs that investigated timing have provided relevant information and tools which, if added to clinical judgment, will contribute to opportune dialysis interventions and improve the survival of this population. So far, given the low-moderate certainty evidence observed in the main outcomes, decisions regarding the optimal timing of KRT should remain based on individual patients' characteristics and clinician judgment.

Implications for research

Given the persistently high death rate among critically ill AKI patients, it would be important to accurately determine the effect of timing of KRT on death. In view of the inconsistencies observed in the main outcomes and the inability to assess all possible causes of heterogeneity, it would be advisable to perform a propensity-based analysis between patients in the early strategy and those who did not receive KRT in the standard group to define whether these patients could have had a better outcome (Bouchard 2020). In addition, KRT intensity during therapy needs to be rigorously evaluated.

Although recent studies would seem to favour delayed KRT initiation, there are likely to be limited to how long KRT can be safely delayed. However, the optimal point in time beyond which the benefits of KRT can be maintained is not known. Therefore, adequately-powered RCTs should include appropriate and reproducible criteria to define the optimal time of KRT are needed. At present, five ongoing RCTs (CRTSAKI 2021; Maiwall 2018; NCT00837057; NCT02937935; NCT03343340) in this area will provide more answers that will guide clinical practice.

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Fayad AI, Buamscha DG, Ciapponi A. Timing of renal replacement therapy initiation for acute kidney injury. *Cochrane Database of Systematic Reviews* 2018, Issue 12. Art. No: CD010612. [DOI: 10.1002/14651858.CD010612.pub2]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

AKIKI 2015

Study characteristics	
Methods	• Study design: parallel, open-label RCT • Duration of study: September 2013 to January 2016 • Duration of follow-up: 60 days
Participants	• Setting: multicentre (31 centres) • Country: France • Critically ill patients ≥ 18 years with AKI stage 3 (KDIGO classification) requiring invasive mechanical ventilation, catecholamine infusion (epinephrine or norepinephrine) or both

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AKIKI 2015 *(Continued)*

- Number: intervention group (311); control group (308)
- Mean age ± SD (years): intervention group (64.8 ± 14.2); control group (67.4 ±13.4)
- Sex (M/F): intervention group (209/103); control group (198/110)
- Exclusion criteria: severe laboratory abnormalities: BUN > 112 mg/dL (40 mmol/L); serum potassium >6 mmol/L or >5.5 mmol/L despite medical treatment; pH < 7.15, $PaCO_2$< 35 mmHg or mixed acidosis ($PaCO_2$ ≥50 mmHg or more without the possibility of increasing alveolar ventilation); acute pulmonary oedema; pre-existing severe CKD (CrCl < 30 mL/min); AKI caused by urinary tract obstruction or renal vessel obstruction or tumour lysis syndrome or thrombotic microangiopathy or acute glomerulopathy; poisoning by a dialyzable agent; child C liver cirrhosis; cardiac arrest without awakening; moribund state (patient likely to die within 24h); patient having already received KRT and kidney transplant

Interventions	KRT modalities • IHD, CKRT or both Intervention group • Early-strategy group: KRT was initiated as soon as possible after randomisation within 6 hours after documentation of KDIGO stage 3 Control group • Delayed-strategy group: KRT was initiated only in case of occurrence of one or more of the following events developed above or if oliguria or anuria lasted for more than 72 hours after randomisation Co-interventions • Not reported
Outcomes	Primary outcomes • Death at day 28 and day 60 Secondary outcomes • Patients requiring at least a KRT in the "waiting" strategy (%) • Mechanical ventilation-free days • Vasopressors-free days • KRT-free days • Length of ICU stay • Length of hospital stay • Nosocomial infection • Adverse events potentially related to the AKI or KRT • Dependence on KRT at days 28 and 60
Notes	• Funding source: supported by a grant from the Programme Hospitalier de Recherchere Clinique National, 2012 (AOM 12456), funded by the French Ministry of Health.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients randomly assigned to one of the two treatment groups by means of a centralized, computer-generated method
Allocation concealment (selection bias)	Low risk	Central allocation process

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AKIKI 2015 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement (for kidney recovery was unclear risk but for death was low risk)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete outcome data were reported
Selective reporting (reporting bias)	Low risk	The study reported death, kidney function recovery and adverse events
Other bias	Low risk	Funding sources were reported (not for profit funding)

Bouman 2002

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: May 1998 to March 2000 • Duration of follow-up: 28 days
Participants	• Setting: multicentre (2 centres) • Country: The Netherlands • Patients with circulatory and respiratory insufficiency and early AKI who need CKRT; CrCl < 20 mL/min, and oliguria < 180 mL/6 hours despite fluid resuscitation; circulatory support and furosemide; early timing: < 12 hours inclusion; late timing: BUN > 40 mmol/L or severe pulmonary oedema • Number: intervention group 1 (35); intervention group 2 (35), control group (36) • Mean age ± SD (years): intervention group 1 (68 ± 13); intervention group 2 (70 ± 10); control group (67 ± 13) • Sex (M/F): intervention group 1 (21/14); intervention group 2 (20/15); control group (23/13) • Exclusion criteria: pre-existing kidney disease with CrCl < 30 mL/min; AKI caused by permanent occlusion or surgical lesion of the renal artery; GN, interstitial nephritis, or vasculitis; postrenal obstruction; CHILD class C liver cirrhosis; AIDS with a CD4 count < 0.05 x 10^9/L; non-witnessed arrest with Glasgow Coma Score < 5; haematological malignancy with neutrophils < 0.05 x 10^9/L; no haemofiltration machine free for use at time of inclusion arrest with Glasgow Coma Score < 5; haematological malignancy with neutrophils < 0.05 x 10^9/L; no haemofiltration machine free for use at time of inclusion

Interventions	KRT modality
	• CVVHF
	  ○ Haemofilter: cellulose triacetate hollow-fibre
	  ○ Replacement fluid: post-dilution mode with bicarbonate solution
	  ○ Anticoagulation: heparin or nadroparin
	Intervention group 1
	• Early + high volume HF: intervention started within 12 hours after time of inclusion, and the UF flow rate was high (prescribed dose > 72 L/day and delivered dose 48.2 mL/kg/hours)
	Intervention group 2

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Bouman 2002 *(Continued)*

- Early + low-volume HF: intervention started within 12 hours after time of inclusion, and the UF flow rate was low (prescribed dose 24 to 36 L/day and 19 to 20 mL/kg/hour)

Control group

- Late + low-volume HF: intervention started when the patients fulfilled the conventional criteria for KRT
  - Urea level > 40 nmol/L, potassium > 6.5 mmol/L or severe pulmonary oedema, and the UF flow rate was 24 to 36 L/day and the delivered dose 19 to 20 mL/kg/hour

Co-interventions

- Not reported

Outcomes	Primary outcomes • Death at day 28 • Recovery of kidney function Secondary outcomes • ICU survival • Hospital survival • Duration of mechanical ventilation • Length of ICU stay • Length of hospitalisation
Notes	• Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients randomly assigned to one of the two treatment groups using computer-generated method
Allocation concealment (selection bias)	Low risk	Treatment assignments were kept in numbered, sealed opaque envelopes that were opened at the time of enrolment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement (for kidney recovery was unclear risk but for death was low risk)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete outcome data were reported
Selective reporting (reporting bias)	Low risk	The study reported death, kidney function recovery and adverse events
Other bias	Unclear risk	Insufficient information to permit judgement

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EARLYRRT 2018

Study characteristics	
Methods	• Study design: parallel, open-label RCT • Duration of study: November 2012 to November 2014 • Duration of follow-up: 28 days
Participants	• Setting: single centre • Country: Thailand • Critically ill patients ≥ 18 years diagnosed with AKI by RIFLE criteria; high plasma NGAL ≥ 400 ng/mL • Number: intervention group (20); control group (20) • Mean age ± SD (years): 66.8 ±15.9 years • Sex (M/F): 22/18 • Exclusion criteria: life expectancy < 24 hours; kidney failure; SCr > 2 mg/dL in males or > 1.5 mg/dL in females; previous kidney transplantation and pregnancy

Interventions	KRT modality
	• CKRT
	Intervention group
	• Early-strategy group: CKRT was started within 12 hours after randomisation
	Control group
	• Standard-strategy group: CKRT was started when the patients fulfilled the following criteria:
	  ○ Severe metabolic acidosis (pH < 7.20)
	  ○ Hyperkalaemia (> 6.2 mmol/L)
	  ○ Severe pulmonary oedema refractory to diuretics
	  ○ Persistent oliguria or anuria and urea > 40 mg/dL

Outcomes	Primary outcomes • Death at day 28 Secondary outcomes on day 28 after randomisation • Ventilator-free days • ICU-free days • Dialysis-dependent • Fluid balance • Recovery of kidney function • Adverse events (KRT-related complications).
Notes	• Funding source: financial support was provided by Ratchadapiseksomphot endowment fund, Faculty of Medicine, King Chulalongkorn University • The study was facilitated by Excellence Center for critical Care Nephrology, King Chulalongkorn Memorial Hospital

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation with sequentially numbered containers into two groups, using computer-generated method

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EARLYRRT 2018 *(Continued)*

Allocation concealment (selection bias)	Low risk	Central allocation process
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement (for kidney recovery was unclear risk but for death was low risk)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete outcome data were reported
Selective reporting (reporting bias)	Low risk	The study reported death, kidney function recovery and adverse events
Other bias	Low risk	Quote: "Alere provided pNGAL kits for use in this study. The company had no influence on the study design or analysis or on the content of this article."

ELAIN 2016

Study characteristics	
Methods	• Study design: parallel, open-label RCT • Duration of study: August 2013 to July 2015 • Duration of follow-up: 90 days
Participants	• Setting: single centre • Country: Germany • Critically ill patients ≥ 18 years with AKI stage 2 (2-fold increase in SCr from baseline or urinary output < 0.5 mL/kg ≥ 12 hours) despite optimal resuscitation; plasma NGAL > 150 ng/mL • Number: intervention group (112); control group (119) • Mean age ± SD (years): intervention group (65.7 ± 13.5); control (68.2 ± 12.7) • Sex (M/F): intervention group (78/34); control (68/51) • Exclusion criteria: pre-existing CKD (GFR < 30 mL/min) previous KRT; AKI caused by permanent occlusion or surgical lesion of the renal artery; GN; interstitial nephritis or vasculitis; AKI caused by postrenal obstruction or haemolytic uraemic syndrome or thrombocytopenic purpura; pregnancy; prior kidney transplantation; hepatorenal syndrome; AIDS with a CD4 count of < 0.05 x 10 E/L; haematological malignancy with neutrophils < 0.05 x 10 E/L; non-HF machine-free for use at the moment of inclusion; participation in another interventional clinical study

Interventions	KRT modality
	• CVVHDF
	  ◦ Replacement fluid: pre-dilution mode
	  ◦ Regional anticoagulation with citrate
	Intervention group
	• Early initiation of CKRT: intervention was started within 8 hours of diagnosis of stage 2 of the KDIGO classification (urine output < 0.5 mL/kg/hour for ≥ 12 hours or 2-fold increase in SCr compared with baseline)

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ELAIN 2016 *(Continued)*

	Control group • Delayed initiation of CKRT: intervention started within 12 hours of stage 3 of the KDIGO classification (urine output < 0.3 mL/kg/hour for ≥ 24 hours and or 3-fold increase in SCr compared with baseline) Co-interventions • Not reported
Outcomes	Primary outcomes • Death at 90 days Secondary outcomes • Death at day 28 and 60 • Clinical evidence of organ dysfunction (daily SOFA score) • Recovery of kidney function • ICU and hospital length of stay • Markers of inflammation (IL6, IL8, IL10, IL18, and macrophage migration inhibitory factor)
Notes	• Funding source: Else-Kroner Fresenius Stiftung (2013_A46 to A.Z.)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomly assigned using computer-generated method
Allocation concealment (selection bias)	Low risk	Each patient received a study identification number and treatment allocation at enrolment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement (for kidney recovery was unclear risk but for death was low risk)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The outcome measurement unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete outcome data were reported
Selective reporting (reporting bias)	Low risk	The study reported death, kidney function recovery and adverse events
Other bias	Low risk	Quote: "The study sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication"

FST 2018

Study characteristics

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FST 2018 *(Continued)*

Methods	• Study design: prospective, open-label RCT • Duration of study: March 2016 to July 2017 • Duration of follow-up: 28 days
Participants	• Setting: multicentre (5 ICUs) • Country: Thailand • Critically ill patients ≥ 18 years with AKI at any stage by KDIGO criteria, FST-non-responsive (urine output < 200 mL for the subsequent 2 hours) • Number: intervention group (58); control group (60) • Mean age ± SD (years): intervention group (67.5 ± 15.0); control group (66.7 ± 16.7) • Sex (M/F): intervention group (29/29); control group (29/3) • Exclusion criteria: patients with SCr ≥ 2 mg/dL (male) or ≥ 1.5 mg/dL (female); history of kidney allograft; pregnancy; allergy or known sensitivity to loop diuretics; moribund patients with expected death within 24 hours or whose survival to 28 days was unlikely due to uncontrollable comorbidity; patients with advanced directives who issued the desire not to be resuscitated; prior treatment with KRT within 30 days; serum albumin < 2 g/dL; patients receiving extracorporeal membrane oxygenation or circulatory assistance
Interventions	KRT modality • CVVH PIKRT HD Early KRT group • Initiation of KRT was started within 6 hours of randomisation Standard KRT group • KRT was initiated only if one of the following criteria were met: BUN ≥ 100 mg/dL, serum potassium > 6 mmol/L, serum bicarbonate < 12 mmol/L or pH < 7.15, $PaCO_2/FIO_2$ ratio < 200, or chest radiograph compatible with pulmonary oedema Co-interventions • Not reported
Outcomes	Primary outcomes • Compliance with the study protocol for > 90% of patients • Ability to use FST to differentiate the KRT rate in FST responders and standard group of nonresponders 50% • Successful randomisation of FST nonresponder • Separation of timing of KRT initiation between the early and standard KRT groups for at least 24 hours • Less than 10% lost to follow-up Secondary outcomes • Death at day 28 • Fluid balance at day 7 • ICU-free days • Mechanical ventilator-free days • KRT-free days • Length of ICU stay and hospital stay • Kidney recovery • Dialysis requirement on day 28 • Proportion of patients free from KRT on days 0, 3, and 7 • Nonrenal SOFA score on days 0, 3, and 7 • KRT-related adverse events

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FST 2018 *(Continued)*

	• Vascular access-related adverse events Exploratory endpoints • Biomarkers: plasma NGAL and Ang2, and NT-proBNP on days 0, 3, and 7
Notes	• Funding source: supported by the Excellence Center for Critical Care Nephrology, King Chulalongkorn Memorial Hospital, funded by The National Kidney Foundation of Thailand

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomly assigned using computer-generated method
Allocation concealment (selection bias)	Low risk	Central allocation process
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement (for kidney recovery was unclear risk but for death was low risk)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The outcome measurement unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete outcome data were reported
Selective reporting (reporting bias)	Low risk	The study reported death, kidney function recovery and adverse events
Other bias	Low risk	Funding sources were reported (not for profit funding)

IDEAL-ICU 2014

Study characteristics

Methods	• Study design: parallel open-label RCT • Study duration: July 2012 to October 2016 • Duration of follow-up: 90 days
Participants	• Setting: multicentre (22 university teaching hospitals and 7 general hospitals) • Country: France • Critically ill patients ≥ 18 years with AKI (RIFLE-F stage) and septic shock • Number: intervention group (246); control group (242) • Mean age ± SD (years): intervention group (69.3 ± 11.6); control group (68.7 ± 12.8) • Sex (M/F): intervention group (142/104); control group (154/88) • Exclusion criteria: chronic KRT; obstructive AKI; need for emergency KRT before randomisation (hyperkalaemia > 6.5 mmol/L, metabolic acidosis with pH < 7.15 or extravascular fluid overload refractory to diuretics with pulmonary oedema); pregnancy; patient is moribund with expected death within 24 hours; patients for whom survival to 28 days is unlikely due to an uncontrollable comorbidity (cardiac, pulmonary or hepatic end-stage disease, hepatorenal syndrome, poorly controlled cancer, se-

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IDEAL-ICU 2014 *(Continued)*

	vere post-anoxic encephalopathy); patients with advance directives issued expressing the desire not to be resuscitated; patient under tutorship, curatorship or judicial protection

Interventions	KRT modality
	• Continuous and intermittent
	Intervention group
	• Early KRT: initiation of KRT immediately after the diagnosis of AKI-failure stage (RIFLE classification) maximum of 12 hours
	Control group
	• Delayed KRT: KRT was initiated 48 hours after the diagnosis of AKI-failure stage when the patients fulfilled the following criteria
	  ○ Serum potassium ≥ 6.5 mmol/L
	  ○ pH ≤ 7.15
	  ○ Severe pulmonary oedema refractory to diuretics
	  ○ No kidney function recovery 48 hours after the diagnosis of AKI-failure stage

Outcomes	Primary outcome • Death from any cause at day 90 after randomisation Secondary outcomes • Death at 28 days and 180 days • Number of days free of KRT at 28 days • Number of days free of mechanical ventilation at 28 days • Number of days free of vasopressors at 28 days • ICU and hospital length of stay • QoL at day 90 and 1 year (EQ-5D questionnaire) • Adverse events: episodes of metabolic disorders, arrhythmia, pulmonary oedema, hypotension, haemorrhage • KRT dependence at hospital discharge
Notes	• Founding source: supported by grant from the Programme Hospitalier de Recherchere Clinique National (A00519), funded by the French Ministry of Health

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomly assigned to the early or delayed-strategy group in a 1:1 ratio by means of an online response system (Tenalea software)
Allocation concealment (selection bias)	Low risk	Central allocation process
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement (for kidney recovery was unclear risk but for death was low risk)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The outcome measurement is not likely to be influenced by lack of blinding

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IDEAL-ICU 2014 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete outcome data were reported
Selective reporting (reporting bias)	Low risk	The study reported death, kidney function recovery and adverse events
Other bias	Low risk	Funding sources were reported (not for profit funding)

STARRT-AKI 2019

Study characteristics	
Methods	• Study design: parallel, open-label RCT • Duration of study: October 2015 to December 2019 • Duration of follow-up: 90 days
Participants	• Setting: multicentre (168 centres) • Country: 15 countries • Critically ill patients ≥ 18 years and AKI (KDIGO stage 2 or 3) • Number: intervention group (1465); control group (1462) • Mean age ± SD (years): intervention group (64.6 ± 14.3); control group (63.7 ± 13.4) • Sex (M/F): intervention group (995/470); control group (995/467) • Exclusion criteria: lack of commitment to ongoing life support, including KRT; presence of an intoxication requiring extracorporeal removal; KRT within the previous 2 months (either acute or chronic KRT); clinical suspicion of renal obstruction, rapidly progressive GN, or acute interstitial nephritis; pre-hospitalisation eGFR < 20 mL/min/1.73 m^2; clinicians caring for patient believes that immediate KRT is absolutely mandated; clinicians caring for patient believe that deferral of KRT initiation is mandated; patient or substitute decision maker is unable to provide consent within 12 hours of determination of study eligibility

Interventions	KRT modality
	• CVVH, IHD, or both
	Intervention group
	• Accelerated KRT initiation: start of KRT within 12 hours of the patient fulfilling study eligibility
	Control group
	• Standard KRT initiation: start of KRT when one of the following conditions develop:
	  ◦ Serum potassium ≥ 6.0 mmol/L
	  ◦ Serum bicarbonate ≤ 12 mmol/L
	  ◦ PaO_2/FiO_2 ≤ 200 with infiltrates on chest radiograph compatible with pulmonary oedema
	  ◦ Volume overload and/or AKI persisted > 72 hours following the time of randomisation
	Co-interventions
	• Not reported

Outcomes	Primary outcome • Death at day 90 Secondary outcomes

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STARRT-AKI 2019 *(Continued)*

- Dialysis-dependent at day 90
- Composite of death or KRT dependence at day 90
- Sustained reduction of kidney function (< 75% baseline eGFR) at day 90
- Death in ICU at day 28
- Death during hospitalisation
- Days free of KRT at 90 days
- Mechanical ventilation-free days at day 28
- Vasoactive therapy-free days at day 28
- ICU-free days at day 28
- Hospitalisation-free days at day 28
- QoL at day 28 and day 365
- Health care costs
- Adverse events
- Adverse events related to KRT and vascular access

Notes	• This study was supported by grants from the Canadian Institutes of Health Research; Baxter Healthcare Corporation, the National Health Medical Research Council of Australia, the Health Research Council of New Zealand, and the Health Technology Assessment Program of the United Kingdom National Institute of Health Research

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomly 1:1 to accelerated versus standard initiation of KRT with variable block sizes (2 and 4) and stratified by centre using a centralised concealed web-based randomisation system
Allocation concealment (selection bias)	Low risk	Central allocation process
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement (for kidney recovery was unclear risk but for death was low risk)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The outcome measurement unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete outcome data were reported
Selective reporting (reporting bias)	Low risk	The study reported death, kidney function recovery and adverse events
Other bias	Low risk	Quote: "The funding organizations and partners were not involved in the design, implementation, management, analysis, and interpretation of the results".

STARRT-AKI Pilot 2013

Study characteristics

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STARRT-AKI Pilot 2013 *(Continued)*

Methods	• Study design: parallel, open-label RCT • Duration of study: May 2012 to November 2013 • Duration of follow-up: 90 days
Participants	• Setting: multicentre (12 ICUs) • Country: Canada • Critically ill patients with severe AKI defined by the presence of 2 of the following 3 criteria: a 2-fold increase in SCr from baseline, urine output < 6 mL/kg in the preceding 12 hours; whole-blood NGAL ≥ 400 ng/mL; absence of urgent indications for KRT initiation (defined as serum potassium ≤ 5.5 mmol/L and serum bicarbonate ≥ 15 mmol/L); low likelihood of volume-responsive AKI; defined as central venous pressure ≥ 8 mm Hg • Number: intervention group (48); control group (52) • Mean age ± SD (years): intervention group (62.2 ± 11.9); control group (63.9 ± 13.6) • Sex (M/F): intervention group (35/13); control group (37/15) • Exclusion criteria: lack of commitment to ongoing life support, including KRT; presence of an intoxication requiring extracorporeal removal; KRT within the previous 2 months; clinical suspicion of renal obstruction, rapidly progressive GN, or interstitial nephritis; pre-hospitalisation eGFR < 30 mL/min/1.73 m^2; the passage of > 48 hours since doubling of baseline SCr; clinician(s) caring for patient believes that immediate KRT is absolutely mandated; clinician(s) caring for patient believes that deferral of KRT initiation is mandated; patient or substitute decision maker is unable to provide consent within 12 hours of determination of study eligibility

Interventions	KRT modality
	• CVVH, IHD, or both
	Intervention group
	• Accelerated KRT initiation: start of KRT within 12 hours of the patient fulfilling study eligibility
	Control group
	• Standard KRT initiation: start of KRT when one of the following conditions develop:
	  ○ Serum potassium ≥ 6.0 mmol/L
	  ○ Serum bicarbonate ≤ 10 mmol/L
	  ○ PaO_2/FiO_2 < 200 with infiltrates on chest radiograph compatible with pulmonary oedema
	  ○ AKI persisted for 72 hours
	Co-interventions
	• Not reported

Outcomes	• Death in ICU • Death in hospital • Death by day 90 • Alive and dialysis-dependent at day 90 • Duration of ICU stay among survivors • Duration of hospitalisation among survivors • Adverse events
Notes	• Founding source: this study was funded by the Canadian Institutes of Health Research and the University of Alberta Hospital Foundation.

Risk of bias

Bias	Authors' judgement	Support for judgement

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STARRT-AKI Pilot 2013 *(Continued)*

Random sequence generation (selection bias)	Low risk	Patients randomly assigned to one of two treatments using computer-generated method
Allocation concealment (selection bias)	Low risk	Treatment assignments were kept in numbered, sealed opaque envelopes that were opened in numeric sequence at the time of enrolment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement (for kidney recovery was unclear risk but for death was low risk)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete outcome data were reported
Selective reporting (reporting bias)	Low risk	The study reported death, kidney function recovery and adverse events
Other bias	Low risk	Quote: "Alere provided the triage MeterPro that was used to measure whole-blood NGAL The founders have no influence on the design, analysis and interpretation of the results."

Sugahara 2004

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: January 1995 to December 1997 • Duration of follow-up: 14 days
Participants	• Setting: single-centre • Country: Japan • Critically ill patients with AKI following coronary artery bypass graft who received KRT when hourly urinary output became ≤ 30 mL/hour and SCr increased at the rate ≥ 0.5 mg/dL/day • Number: intervention group (18); control group (18) • Mean age ± SD (years): intervention group (65 ± 3); control group (64 ± 2) • Sex (M/F): intervention group (9/5); control group (9/5) • Exclusion criteria: patients who were pregnant; severe hepatic dysfunction (serum bilirubin level ≥ 5.0 mg/dL); mental disorders; cancer; patients with proteinuria ≥ 2.0 g or SCr ≥ 1.4 mg/dL before surgery
Interventions	KRT modality • CVVH ○ Anticoagulation: nafamostat mesylate Intervention group • Early-start CKRT: when hourly urinary output became < 30 mL/hour for 3 consecutive hours (or daily urinary output ≤ 750 mL) • Conventional-start CKRT: When hourly urinary output became < 20 mL/hour for 2 consecutive hours (or daily urinary output ≤ 500 mL)

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Sugahara 2004 *(Continued)*

	Co-interventions • Not reported
Outcomes	Primary outcome • Survival at day 14 Secondary outcome • Recovery of kidney function
Notes	• Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement Quote: "All patients were divided randomly into two groups"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Outcome measurement was unlikely to be influenced by lack of blinding (for kidney recovery was unclear risk but for death was low risk)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	> 20% of included patients not reported
Selective reporting (reporting bias)	Low risk	The study reported survival and kidney function recovery
Other bias	Unclear risk	Insufficient information to permit judgement

Tang 2016

Study characteristics

Methods	• Study design: parallel RCT • Duration of study: June 2012 to December 2014 • Duration of follow-up: 14 days
Participants	• Setting: single centre • Country: China • Patients with sepsis and AKI (AKIN-AKI stage 2 or 3) who need CKRT • Number: intervention group 1 (23); intervention group 2 (23); control group (46) • Mean age ± SD (years): intervention group 1 and 2 (54.3 ± 4.7); control group (57.9 ± 5.2)

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Tang 2016 *(Continued)*

- Sex (M/F): intervention group 1 and 2 (21/25); control group (24/22)
- Exclusion criteria: pre-existing kidney disease; chronic liver disease; pregnancy; mental disease; infection without clear focus

Interventions	KRT modality • CVVHD Intervention group 1 • Early-start CKRT: < 48 hours after randomisation Intervention group 2 • Delayed-start CKRT: > 48 hours after randomisation Control group • Standard drug intervention Co-interventions • Not reported
Outcomes	• Survival at day 15 and after 15 days
Notes	• Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Outcome measurement was unlikely to be influenced by lack of blinding (for death was low risk)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete outcome data were reported
Selective reporting (reporting bias)	High risk	The study reported only one outcome (survival)
Other bias	Unclear risk	Insufficient information to permit judgement

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Xia 2019

Study characteristics	
Methods	• Study design: prospective, open-label RCT • Duration of study: January 2013 to June 2017 • Duration of follow-up: until day 28 after randomisation
Participants	• Setting: single-centre • Country: China • Critically ill patients with AKI and sepsis; ≥ 18 years • Number: intervention group (30); control group (30) • Mean age ± SD (years): intervention group (65.4 ± 12.3); control group (67.49 ± 10.8) • Sex (M/F): intervention group (15/15); control group (18/12) • Exclusion criteria: patients with malignant tumour; CKD; blood disease, thyroid disease, and long-term immunosuppression; drugs or glucocorticoids; contraindications to CKRT treatment; breast-feeding or pregnant

Interventions	KRT modality
	• CKRT
	Intervention group
	• Early-strategy group: AKI and urinary NGAL level > 1310 ng/mL; CKRT was started within 12 hours after randomisation
	Control group
	• Standard-strategy group: AKI and NGAL < 1310 ng/mL; CKRT intervention started when the patients fulfilled the following criteria
	  ○ Severe metabolic acidosis (pH < 7.20, blood HCO_3 < 12 mmol/L)
	  ○ Hyperkalaemia > 6.5 mmol/L
	  ○ Water intoxication (with manifestations of heart failure or pulmonary oedema)

Outcomes	Primary outcome • Death at day 28 Secondary outcomes • Recovery of kidney function • Mechanical ventilation time • ICU stay • Hospital stay • Dialysis dependence
Notes	• This study was supported by the Science and Technology Project, funded by Health Bureau of Shanxi Providence

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement Quote: "All patients were divided randomly into two groups"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement

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Xia 2019 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement (for kidney recovery was unclear risk but for death was low risk)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete outcome data were reported
Selective reporting (reporting bias)	Low risk	The study reported death, kidney function recovery, dialysis dependence, ICU and hospital stay.
Other bias	Low risk	Not for profit funding

Yin 2018

Study characteristics	
Methods	• Study design: prospective, RCT • Duration of study: June 2015 to May 2017 • Duration of follow-up: until day 90 after randomisation
Participants	• Setting: single-centre • Country: China • Critically ill patients with septic shock and AKI; ≥ 18 years • Number: intervention group (33); control group (30) • Mean age ± SD (years): intervention group (58.6 ± 18.53); control group (63.20 ± 9.66) • Sex (M/F): intervention group (23/10); control group (19/11) • Exclusion criteria: malignant tumour; hypoxic ischaemic encephalopathy; hepatic disease; CKD; blood disease; contraindications to CKRT treatment; breastfeeding or pregnant
Interventions	KRT modality • CKRT Intervention group • Early-strategy group: patient with AKI RIFLE-F stage CKRT started within 12 hours after randomisation Control group • Standard-strategy group: patient with AKI RIFLE-F stage CKRT started ≥ 48 hours after randomisation
Outcomes	Primary outcome • Death at days 28, 60 and 90 Secondary outcome • Survival • Mechanical ventilation time • ICU stay

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Yin 2018 *(Continued)*

	• Hospital stay
Notes	• Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement Quote: "All patients were divided randomly into two groups"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Insufficient information to permit judgement (for kidney recovery was unclear risk but for death was low risk)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete outcome data were reported
Selective reporting (reporting bias)	Low risk	The study reported death, ICU and hospital stay
Other bias	Unclear risk	Insufficient information to permit judgement

AIDS: acquired immune deficiency syndrome; AKI: acute kidney injury; AKIN: Acute Kidney Injury Network; Ang2: angiopoietin-2; BUN: blood urea nitrogen; CKD: chronic kidney disease; CrCl: creatinine clearance; CKRT: continuous kidney replacement therapy; CVVH: continuous venovenous haemofiltration; CVVHDF: continuous venovenous haemodiafiltration; FST: furosemide stress test; HD: haemodialysis; HF - haemofiltration; (e)GFR: (estimated) glomerular filtration rate; GN: glomerulonephritis; HF: haemofiltration; ICU: intensive care unit; IHD: intermittent haemodialysis; KDIGO: Kidney Disease: Improving Global Outcomes; KRT: kidney replacement therapy; M/F: male/female; NGAL: plasma neutrophil gelatinase-associated lipocalin; NT-proBNP: N-terminal-pro hormone brain natriuretic peptide; PIKRT: prolonged intermittent kidney replacement therapy; QoL: quality of life; RCT: randomised controlled trial; RIFLE: Risk Injury Failure Loss ESKD; SCr: serum creatinine; SD: standard deviation; SOFA: Sequential Organ Failure Assessment; UF: ultrafiltration

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abe 2010c	Wrong intervention: timing of KRT initiation was not assessed
AKIKI 2 2019	Wrong intervention: delayed arm and more delayed arm
Albino 2014	Wrong intervention: timing of KRT initiation was not assessed
Ambrós Checa 1995	Wrong intervention: timing of KRT initiation was not assessed
Andrade 1997	Wrong intervention: timing of KRT initiation was not assessed (evaluated CAVHF)

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Study	Reason for exclusion
ATN 2005	Wrong intervention: timing of KRT initiation was not assessed (compared the survival and kidney recovery in critically ill patients treated with intensive versus less-intensive KRT)
Augustine 2004	Wrong intervention: timing of KRT initiation was not assessed
Badawy 2013	Wrong intervention: timing of KRT initiation was not assessed (compared the efficacy of CVVHDF and EDD in patients with AKI after cardiac surgery)
Baldwin 2007	Wrong intervention: timing of KRT initiation was not assessed (compared EDD with HF or CVVHF with regard to fluid removal and haemodynamics)
Berg 2007	Wrong intervention: timing of KRT initiation was not assessed
Berger 2004	Wrong intervention: timing of KRT initiation was not assessed
Boussekey 2008	Wrong intervention: timing of KRT initiation was not assessed
Boyle 1995	Wrong intervention: timing of KRT initiation was not assessed
Cole 2001	Wrong intervention: timing of RRT initiation was not assessed
Cole 2002	Outcomes of interest not investigated: evaluated the effect of early and CVVHF on the plasma concentrations of several humoral mediators of inflammation in septic patients
CRITERIA 2012	Wrong intervention: timing of KRT initiation was not assessed
Daud 2006	Wrong intervention: timing of RRT initiation was not assessed
Davenport 1991	Wrong intervention: timing of KRT initiation was not assessed
Davenport 1993a	Wrong intervention: timing of KRT initiation was not assessed
Davies 2008	Wrong intervention: timing of KRT initiation was not assessed
de Pont 2006	Wrong intervention: timing of KRT initiation was not assessed
Durmaz 2003	Wrong population: the presence of AKI was no obligatory condition for enrolment in the early arm
Gabriel 2008	Wrong intervention: timing of KRT initiation was not assessed (compared the role of HVPD to daily HD in patients with AKI; HVPD was not included in this review)
Garcia-Fernandez 2000	Wrong intervention: timing of KRT initiation was not assessed
Gasparovic 2003	Wrong intervention: timing of KRT initiation was not assessed
George 2011	Wrong intervention: timing of KRT initiation was not assessed
Ghani 2006	Wrong intervention: timing of KRT initiation was not assessed
Gillum 1986	Wrong intervention: timing of KRT initiation was not assessed
Haase 2007b	Wrong intervention: timing of KRT initiation was not assessed; high-adsorption CVVHD was not included in this review
Han 2015	Wrong population: the presence of AKI was no obligatory condition for enrolment in the early arm

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Study	Reason for exclusion
HAN-D-OUT 2009	Wrong intervention: timing of KRT initiation was not assessed
HEROICS 2015	Wrong population: the presence of AKI was no obligatory condition for enrolment in the early arm
Hoste 1995	Wrong intervention: timing of KRT initiation was not assessed
Jamale 2013	Wrong population: included patients with AKI, but ICU stay was no obligatory condition for enrolment in the early arm
Jeffrey 1994	Wrong intervention: timing of KRT initiation was not assessed
John 2001	Wrong intervention: timing of KRT initiation was not assessed
Jones 1998	Wrong intervention: timing of KRT initiation was not assessed
Kellum 1998	Wrong intervention: timing of KRT initiation was not assessed
Kielstein 2004	Wrong intervention: timing of KRT initiation was not assessed
Kielstein 2005	Wrong intervention: timing of KRT initiation was not assessed
Kierdorf 1995	Wrong intervention: timing of KRT initiation was not assessed
Klouche 2007	Wrong intervention: timing of KRT initiation was not assessed
Koo 2006	Wrong population: the presence of AKI was no obligatory condition for enrolment in the early arm
Kumar 2004	Wrong intervention: timing of KRT initiation was not assessed
Lentini 2009	Wrong intervention: timing of KRT initiation was not assessed (compared pulse high volume HF and coupled plasma filtration adsorption in septic shock patients)
Manns 1996	Wrong intervention: timing of KRT initiation was not assessed
Maxvold 2000	Wrong intervention: timing of KRT initiation was not assessed
Mehta 2001	Wrong intervention: timing of KRT initiation was not assessed
Meloni 1996	Wrong intervention: timing of KRT initiation was not assessed
Misset 1996	Outcomes of interest not assessed: evaluated the haemodynamic response to IHF and continuous HF in ICU patients with AKI
Morgera 2004	Wrong intervention: timing of KRT initiation was not assessed
Morgera 2006	Wrong intervention: timing of KRT initiation was not assessed
Noble 2006	Wrong intervention: timing of KRT initiation was not assessed
OMAKI 2012	Wrong intervention: timing of KRT initiation was not assessed
Oudemans-van-Straaten 2009a	Wrong intervention: timing of KRT initiation was not assessed
Paganini 1996	Wrong intervention: timing of KRT initiation was not assessed

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Study	Reason for exclusion
Park 2016	Wrong intervention: timing of KRT initiation was not assessed
Payen 2009	Wrong population: the presence of AKI was no obligatory condition for enrolment in the early arm
Pettila 2001	Wrong intervention: timing of KRT initiation was not assessed
Ponce 2011	Wrong intervention: timing of KRT initiation was not assessed
Ponce 2013	Wrong intervention: timing of KRT initiation was not assessed
Pursnani 1997	Wrong population: included patients with AKI, but ICU stay was no obligatory condition for enrolment in the early arm
Ratanarat 2012	Wrong intervention: timing of KRT initiation was not assessed
RENAL 2006	Wrong study design: 2 records of this study assessed timing of CKRT, but were not RCTs (retrospective nested cohort)
RESCUE 2012	Wrong intervention: timing of KRT initiation was not assessed
Ricci 2006	Wrong intervention: timing of KRT initiation was not assessed
Ronco 1999a	Wrong intervention: timing of KRT initiation was not assessed
Ronco 2000a	Wrong intervention: timing of KRT initiation was not assessed
Ronco 2001	Wrong intervention: timing of KRT initiation was not assessed
Saudan 2006	Wrong intervention: timing of KRT initiation was not assessed
Schiffl 1997	Wrong intervention: timing of KRT initiation was not assessed
Schiffl 2002	Wrong intervention: timing of KRT initiation was not assessed
SHARF 2009	Wrong intervention: timing of KRT initiation was not assessed
Stefanidis 1995	Wrong intervention: timing of KRT initiation was not assessed
Storck 1991	Wrong intervention: timing of KRT initiation was not assessed
Tan 2001	Wrong intervention: timing of KRT initiation was not assessed
Tolwani 2008	Wrong intervention: timing of KRT initiation was not assessed
Uehlinger 2005	Wrong intervention: timing of KRT initiation was not assessed
van der Voort 2005	Wrong intervention: timing of KRT initiation was not assessed
Vinsonneau 2006	Wrong intervention: timing of KRT initiation was not assessed
Wynckel 1998	Wrong intervention: timing of KRT initiation was not assessed
Wynckel 2004	Wrong intervention: timing of KRT initiation was not assessed
Zhang 2004a	Wrong intervention: timing of KRT initiation was not assessed

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Study	Reason for exclusion
Zhao 2009a	Wrong intervention: timing of KRT initiation was not assessed
Zimmerman 1999	Wrong intervention: timing of KRT initiation was not assessed

AKI: acute kidney injury; CAVHF: continuous arteriovenous haemofiltration; CVVHDF: continuous venovenous haemodiafiltration; EDD: extended daily dialysis; HD: haemodialysis; HF: haemofiltration; HVPD: high volume peritoneal dialysis; ICU: intensive care unit; IHF: intermittent haemofiltration; KRT: kidney replacement therapy; RCT: randomised controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

CRTSAKI 2021

Study name	CRRT timing in sepsis-associated AKI in ICU (CRTSAKI)
Methods	• Study design: parallel, open-label RCT • Duration of study: expected to last for 4 years; recruitment of participants started in August 2019 • Duration of follow-up: for primary outcome until 90 days from the date of randomisation (day 0)
Participants	• Setting: multicentre (13 ICUs) • Country: China • Health status: critically ill patients with sepsis (sepsis-3) and AKI at stage 2 of KDIGO classification; aged 18 and 90 years • Exclusion criteria: presence of one of the emergent CKRT conditions before randomisation: hyperkalaemia > 6.0 mmol/L or > 5.5 mmol/L persisting despite medical treatment; acute pulmonary oedema due to fluid overload responsible for severe hypoxaemia requiring oxygen flow rate > 5 L/min to maintain a percutaneous oxygen saturation > 95% or a fraction of inspired oxygen > 50% in patients already on invasive or non-invasive mechanical ventilation and despite diuretic therapy; BUN > 112 mg/dL (40 mmol/L); pre-existing severe CKD; previous KRT; prior kidney transplant; AKI caused by permanent postrenal obstruction or surgical lesion of renal vessel; pregnancy; hepatorenal syndrome; AIDS; survival to 90 days is unlikely due to end-stage diseases; moribund with expected death within 24 hours; included in another interventional clinical trial

Interventions	KRT modality
	• CKRT
	Intervention group
	• Early CKRT group: patients will initiate CKRT as fast as possible. A maximum of 8 hours after randomisation
	Control group
	• Delayed CKRT group: patients will initiate CKRT if AKI develops to stage 3 of KDIGO classification or when one of the emergent CKRT conditions after randomisation
	  ◦ Hyperkalaemia > 6.0 mmol/L
	  ◦ Acute pulmonary oedema
	  ◦ BUN > 112 mg/dL (40 mmol/L)

Outcomes	Primary outcome • Death at day 90 Secondary outcomes • Death at day 28 and 1 year • Recovery rate of kidney function by day 28 and 90

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CRTSAKI 2021 *(Continued)*

	• ICU and hospital length of stay • Percentage of receipt of CKRT at least once in the delayed group • Number of days alive without CKRT, mechanical ventilation and vasopressor between day 0 and up to day 90 • SOFA score at day 0, day 1, day 3, day 7, day 14 and day 28 • Impacts on other organ functions (heart, lung, liver) • Rate of complications potentially related to CKRT: (a) major bleeding associated with anticoagulants (b) thrombosis of a large venous axis diagnosed by Doppler ultrasound, (c) catheter-related bloodstream infection (d) thrombocytopenia (< 6.5 mmol/L), (e) hypothermia, (i) hypokalaemia • Cost analysis of CKRT • Duration between randomisation to CKRT initiation • Duration between appearance of at least one of the criteria that initiated CKRT in the delayed group and actual initiation • New biomarkers of AKI • Concentrations of inflammatory mediators in serum in two groups IL1, IL6 and tumour necrosis factor α (TNF-α)
Starting date	5 June 2017
Contact information	xiongxuming9@126.com
Notes	Last update posted: December 2021 Recruitment status: recruiting

Maiwall 2018

Study name	Early versus late sustained low efficiency dialysis in critically ill cirrhotics with septic shock and acute kidney injury: a pilot randomised controlled trial
Methods	• Study design: parallel, open-label RCT • Duration of study: start July 2018 • Duration of follow-up: until day 28 after randomisation
Participants	• Country: India • Health status: cirrhosis with septic shock associated AKI stage 3 AKIN/KDIGO stage 2 • aged 18 to 65 years • Exclusion criteria: < 18 years; severe known cardiopulmonary disease (structural or valvular heart disease, coronary artery disease, COPD); pregnancy; CKD on HD; post renal obstructive AKI; AKI suspected due to GN, interstitial nephritis or vasculitis based on clinical history and urine analysis; already meeting emergency criteria for immediate HD at the time of randomisation (serum potassium > 6 mEq/L, metabolic acidosis pH < 7.12, acute pulmonary oedema, severe volume overload with hypoxaemia non-responsive to diuretic treatment); transferred from other hospitals who have already been on HD before their arrival in the ICU; extremely moribund patients with an expected life expectancy < 24 hours; failure to get informed consent from family members; haemodynamic instability requiring very high dose of vasopressors
Interventions	KRT modality • SLED Intervention group • Early SLED within 6 to 12 hours after randomisation Control group

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Maiwall 2018 *(Continued)*

	• Late SLED when absolute indications will meet
Outcomes	Primary outcome • Transplant-free survival in both groups at day 28 Secondary outcomes • Death related to kidney failure in both groups at day 7 • Death due to kidney failure related in both groups at day 7 • Incidence of intra-dialytic hypotension in both groups at 48 hours • Haemodynamic stability in both groups at 48 hours • Dialysis efficiency as measured by URR in both groups at 48 hours • Achievement of target ultrafiltration goals in both groups at 48 hours • Recovery in kidney function in both groups at day 14 • Duration of ICU stay in both groups at day 28 • Duration of mechanical ventilation in both groups at day 28 • Improvement in SOFA (by 2 points) scores in both groups at day 28 • Improvement in SOFA, Model for End-stage Liver Disease (by 2 points) scores at day 28 • Improvement in Acute Physiology and Chronic Health Evaluation (by 2 points) scores at day 28 • Improvement in lactic acidosis and lactate clearance at 6 initiations of dialysis in both groups at 6 hours • Improvement in lactic acidosis and lactate clearance at 24 hours after initiation of dialysis in both groups at 12 hours • Improvement in lactic acidosis and lactate clearance at 24 hours after initiation of dialysis in both groups at 24 hours
Starting date	19 October 2016
Contact information	rakhi_2011@yahoo.co.in
Notes	Last update posted: 7 March 2019 Recruitment status was: recruiting

NCT00837057

Study name	Early continuous renal replacement therapies (CKRT) in patients with severe sepsis or septic shock with acute kidney injury
Methods	• Study design: RCT • Estimate primary completion date: January 2011 (final data collection date for primary outcome measure)
Participants	• Setting: multicentre (number of sites not reported) • Country: Korea • Health status: patients with severe sepsis or septic shock with AKI who need CKRT for less than 14 days • Number: 60 patients • Age: > 18 years • Exclusion criteria: cirrhosis CHILD class C, CKD or ESKD, high APACHE II & SOFA score at admission; age > 80 years; life expectancy < 3 months (metastatic cancer- hepatoma, lung cancer)
Interventions	Dialysis modality

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NCT00837057 *(Continued)*

	• CVVHF Intervention group • Early timing: AKI or nearly anuria > 2 hours Control group • Late timing: conventional dialysis indication
Outcomes	Primary outcome • Death at 28 days after randomisation Secondary outcomes • Death within the ICU • Death within 90 days of randomisation • Death prior to hospital discharge • Length of ICU stay • The need for and duration of other organ support (90 days)
Starting date	5 February 2009
Contact information	sbhong@amc.seoul.kr
Notes	Last update posted: 5 February 2009 Recruitment status was: not yet recruiting

NCT02937935

Study name	On demand versus protocol-guided kidney replacement therapy for management of stage 3 acute kidney Injury in patients with cirrhosis
Methods	• Study design: parallel, open-label RCT • Estimated study start date: July 1, 2018 • Duration of follow-up: for primary outcome until 14 days from the date of randomisation (day 0)
Participants	• Country: India • Health status: patients with cirrhosis with stage 3 AKI defined as an increase of SCr > 300 fold and > 4 mg/dL; 18 to 65 years • Exclusion criteria: < 18 years; severe known cardiopulmonary disease (structural or valvular heart disease, coronary artery disease, COPD; pregnancy; CKD on HD; post renal obstructive AKI, AKI suspected due to GN, interstitial nephritis or vasculitis based on clinical history and urine analysis; patients already meeting emergency criteria for immediate HD at the time of randomisation (serum potassium > 6 mEq/L metabolic acidosis pH < 7.12, acute pulmonary oedema, severe volume overload with hypoxaemia non-responsive to diuretic treatment); patients transferred from other hospitals who have already been on HD before their arrival in the ICU; extremely moribund patients with an expected life expectancy < 24 hours; failure to get informed consent from family members; haemodynamic instability requiring very high dose of vasopressors
Interventions	Intervention group • Protocol-guided KRT: all patients would be considered for dialysis within 6 hours of randomisation. After randomisation patients would receive dialysis as 3 sessions/week of at least 4 hours with a blood flow > 200 mL/min and a dialysate flow > 500 mL/min in intermittent group and as

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NCT02937935 *(Continued)*

	20 to 25 mL/kg/hour of effluent, by filtration and/or diffusion in continuous form until recovery of kidney function Control group • On-demand KRT: patients would get dialysis only when patient fulfils absolute criteria requiring dialysis, such as metabolic acidosis with pH < 7.2, hyperkalaemia, refractory fluid overload (non-responsive to diuretics) or oliguria with urine output < 0.5 mL/kg for more than 24 to 48 hours from the time of randomisation
Outcomes	Primary outcome • Recovery of kidney function in both groups at day 14 Secondary outcomes • Adverse effects of dialysis in the first session in both groups at 48 hours • Improvement in SOFA (by 2 points) scores in both groups at 48 hours • Improvement in MELD (by 2 points) scores in both groups at 48 hours • Improvement in APACHE (by 2 points) scores in both groups at 48 hours • Change to kidney failure with requirement of maintenance HD at least twice/week in both groups by 4 weeks • Improvement in kidney function in both groups at day 7 • Death in both groups at 1 month • Death in both groups at 3 months • Response to vasoconstrictors in patients with Hepatorenal Syndrome-AKI in both groups at 6, 12 and 24 hours
Starting date	19 October 2016
Contact information	rakhi_2011@yahoo.co.in
Notes	Last update posted: 29 November 2017 Recruitment status was: not yet recruiting

NCT03343340

Study name	Early versus late continuous kidney replacement therapy in acute on chronic liver failure patients with septic shock and acute kidney injury a randomized controlled trial
Methods	• Study design: parallel, open-label RCT • Estimated study start date: September 2017 • Duration of follow-up: for primary outcome until 24 days from the date of randomisation (day 0)
Participants	• Country: China • Health status: patients with acute chronic liver failure and septic shock with AKI; ≥ 18 years • Exclusion criteria: < 18 years; severe known cardiopulmonary disease (structural or valvular heart disease, coronary artery disease, COPD); pregnancy; CKD on HD; hepatorenal syndrome, post-renal obstructive AKI, AKI due to GN, interstitial nephritis or vasculitis; patients already meeting emergency criteria for immediate HD at the time of randomisation (serum potassium > 6 meq/L, metabolic acidosis pH < 7.12, acute pulmonary oedema, severe volume overload with hypoxaemia non-responsive to diuretic treatment); patients transferred from other hospitals who have already been on HD before their arrival in the ICU; extremely moribund patients with an expected life expectancy < 24 hours; failure to get informed consent from family members; haemodynamic instability requiring very high dose of vasopressors

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NCT03343340 *(Continued)*

Interventions	Intervention group • Early CKRT within 6 hours + standard medical therapy Control group • Late CKRT + standard medical therapy
Outcomes	Primary outcome • Transplant-free survival at day 28 Secondary outcomes • Incidence of intradialytic hypotension: decrease in SBP by ≥ 20 mm Hg or a decrease in MAP by 10 mm Hg associated with symptoms at 1 year • Haemodynamic stability: maintenance of MAP on dialysis without an increase in the vasopressors at 1 year • Dialysis efficiency as measured by URR at 48 hours • Recovery in kidney functions defined: increase in urine output > 400 mL/day by 1 year • Duration of mechanical ventilation and ICU stay by 1 year • Improvement in SOFA (by 2 points) scores at 1 year • Improvement in APACHE (by 2 points) scores at 1 year • Improvement in MELD (by 2 points) scores at 1 year • Improvement in lactic acidosis and lactate clearance at 6 hours after initiation of CKRT within 6 hours • Improvement in lactic acidosis and lactate clearance at 12 hours after initiation of CKRT within 12 hours • Improvement in lactic acidosis and lactate clearance at 24 hours after initiation of CKRT within 24 hours
Starting date	17 November 2017
Contact information	rakhi_2011@yahoo.co.in
Notes	Last update posted: 17 November 2017 Recruitment status was: recruiting

AIDS: acquired immune deficiency syndrome; AKI: acute kidney injury; AKIN: Acute Kidney Injury Network; APACHE: Acute Physiology and Chronic Health Evaluation; BUN: blood urea nitrogen; CKD: chronic kidney disease; CKRT/CRRT: continuous kidney/renal replacement therapy; COPD: chronic obstructive pulmonary disease; CVVHF: continuous venovenous haemofiltration; ESKD: end-stage kidney disease; GN: glomerulonephritis; HD: haemodialysis; KDIGO: Kidney Disease: Improving Global Outcomes; KRT - kidney replacement therapy; MAP: mean arterial pressure; MELD: Model for End Stage Liver Disease; RCT - randomised controlled trial; SBP: systolic blood pressure; SCr: serum creatinine; SLED: Sustained Low Efficiency Dialysis; SOFA: Sequential Organ Failure Assessment; URR: urea reduction ratio

DATA AND ANALYSES

Comparison 1. Early versus standard initiation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Death	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1.1 Death at day 30	12	4826	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.87, 1.09]
1.1.2 Death after 30 days	7	4534	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.92, 1.07]
1.2 Death or non-recovery kidney function at day 90	6	4011	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.74, 1.11]
1.3 Recovery of kidney function	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.3.1 Patients free from KRT according to ITT analysis (all patients)	10	4717	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.94, 1.22]
1.3.2 Survivors free from KRT according to ITT after 30 days	10	2510	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.97, 1.07]
1.4 Adverse events	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.4.1 Any adverse event	5	3983	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.90, 1.68]
1.4.2 Hypophosphataemia	1	2927	Risk Ratio (M-H, Random, 95% CI)	1.80 [1.33, 2.44]
1.4.3 Hypotension	5	3864	Risk Ratio (M-H, Random, 95% CI)	1.54 [1.29, 1.85]
1.4.4 Cardiac-rhythm disorder	6	4483	Risk Ratio (M-H, Random, 95% CI)	1.35 [1.04, 1.75]
1.4.5 Infection	5	4252	Risk Ratio (M-H, Random, 95% CI)	1.33 [1.00, 1.77]
1.4.6 Bleeding	6	4358	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.71, 1.18]
1.4.7 Thrombocytopenia	1	106	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.20, 5.35]
1.5 Length of stay	7		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.5.1 Length of stay in ICU	5	4240	Mean Difference (IV, Random, 95% CI)	-1.01 [-1.60, -0.42]
1.5.2 Length of stay in hospital	7	4589	Mean Difference (IV, Random, 95% CI)	-2.45 [-4.75, -0.14]

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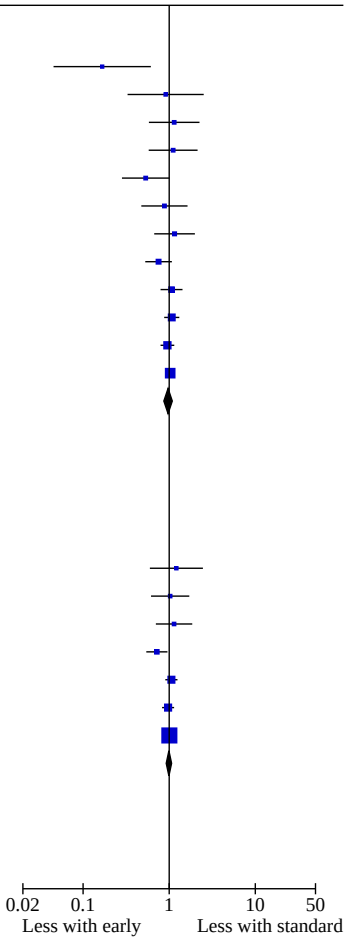
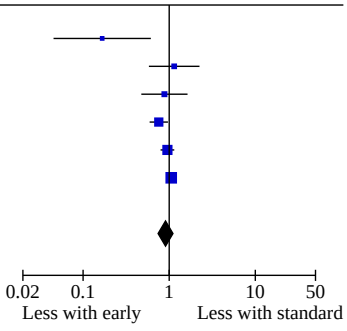
Analysis 1.1. Comparison 1: Early versus standard initiation, Outcome 1: Death

Study or Subgroup	Early initiation Events	Total	Standard initiation Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Death at day 30						
Sugahara 2004	2	14	12	14	0.7%	0.17 [0.05 , 0.61]
Yin 2018	6	33	6	30	1.2%	0.91 [0.33 , 2.52]
Bouman 2002	20	70	9	36	2.6%	1.14 [0.58 , 2.25]
EARLYRRT 2018	10	20	9	20	2.8%	1.11 [0.58 , 2.14]
Tang 2016	8	23	15	23	2.9%	0.53 [0.28 , 1.01]
STARRT-AKI Pilot 2013	13	48	16	52	3.1%	0.88 [0.47 , 1.63]
Xia 2019	15	30	13	30	3.8%	1.15 [0.67 , 1.99]
ELAIN 2016	34	112	48	119	7.9%	0.75 [0.53 , 1.07]
FST 2018	36	58	35	60	10.5%	1.06 [0.79 , 1.43]
IDEAL-ICU 2014	111	246	102	242	16.9%	1.07 [0.87 , 1.31]
AKIKI 2015	129	311	134	308	18.6%	0.95 [0.79 , 1.15]
STARRT-AKI 2019	538	1465	523	1462	29.0%	1.03 [0.93 , 1.13]
Subtotal (95% CI)		**2430**		**2396**	**100.0%**	**0.97 [0.87 , 1.09]**
Total events:	922		922			
Heterogeneity: Tau² = 0.01; Chi² = 15.42, df = 11 (P = 0.16); I² = 29%						
Test for overall effect: Z = 0.53 (P = 0.60)						
1.1.2 Death after 30 days						
Yin 2018	12	33	9	30	1.0%	1.21 [0.60 , 2.46]
STARRT-AKI Pilot 2013	18	48	19	52	1.9%	1.03 [0.62 , 1.71]
Bouman 2002	31	70	14	36	2.1%	1.14 [0.70 , 1.85]
ELAIN 2016	44	112	65	119	6.2%	0.72 [0.54 , 0.95]
IDEAL-ICU 2014	138	246	128	242	17.5%	1.06 [0.90 , 1.25]
AKIKI 2015	150	311	153	308	17.8%	0.97 [0.83 , 1.14]
STARRT-AKI 2019	643	1465	639	1462	53.5%	1.00 [0.93 , 1.09]
Subtotal (95% CI)		**2285**		**2249**	**100.0%**	**0.99 [0.92 , 1.07]**
Total events:	1036		1027			
Heterogeneity: Tau² = 0.00; Chi² = 6.41, df = 6 (P = 0.38); I² = 6%						
Test for overall effect: Z = 0.22 (P = 0.83)						
Test for subgroup differences: Chi² = 0.11, df = 1 (P = 0.74), I² = 0%						



Analysis 1.2. Comparison 1: Early versus standard initiation, Outcome 2: Death or non-recovery kidney function at day 90

Study or Subgroup	Early initiation Events	Total	Standard initiation Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Sugahara 2004	2	14	12	14	2.2%	0.17 [0.05 , 0.61]
Bouman 2002	20	70	9	36	6.9%	1.14 [0.58 , 2.25]
STARRT-AKI Pilot 2013	13	48	16	52	8.0%	0.88 [0.47 , 1.63]
ELAIN 2016	52	112	73	119	22.8%	0.76 [0.59 , 0.97]
AKIKI 2015	129	311	134	308	26.9%	0.95 [0.79 , 1.15]
STARRT-AKI 2019	728	1465	688	1462	33.3%	1.06 [0.98 , 1.14]
Total (95% CI)		**2020**		**1991**	**100.0%**	**0.91 [0.74 , 1.11]**
Total events:	944		932			
Heterogeneity: Tau² = 0.03; Chi² = 14.79, df = 5 (P = 0.01); I² = 66%						
Test for overall effect: Z = 0.97 (P = 0.33)						
Test for subgroup differences: Not applicable						



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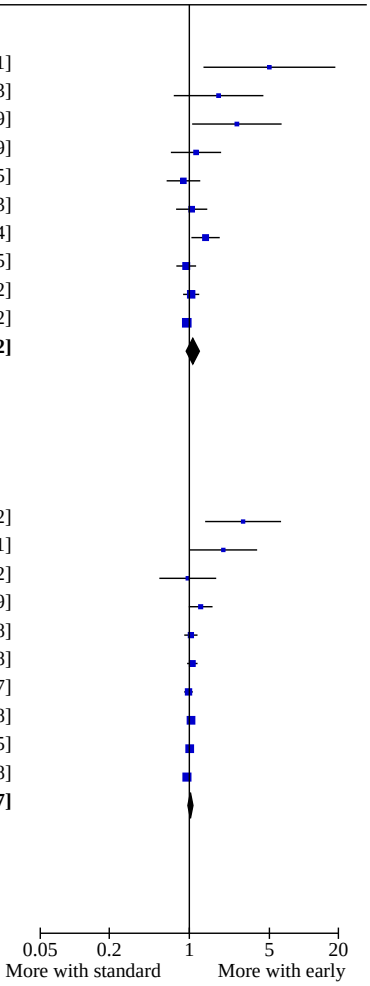
Analysis 1.3. Comparison 1: Early versus standard initiation, Outcome 3: Recovery of kidney function

Study or Subgroup	Early initiation Events	Total	Standard initiation Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Patients free from KRT according to ITT analysis (all patients)						
Sugahara 2004	10	14	2	14	1.0%	5.00 [1.33 , 18.81]
EARLYRRT 2018	9	20	5	20	2.0%	1.80 [0.73 , 4.43]
Xia 2019	13	30	5	30	2.0%	2.60 [1.06 , 6.39]
FST 2018	21	58	19	60	5.4%	1.14 [0.69 , 1.89]
Bouman 2002	38	70	22	36	9.5%	0.89 [0.63 , 1.25]
STARRT-AKI Pilot 2013	30	48	31	52	10.5%	1.05 [0.77 , 1.43]
ELAIN 2016	60	112	46	119	11.6%	1.39 [1.04 , 1.84]
IDEAL-ICU 2014	106	246	111	242	16.1%	0.94 [0.77 , 1.15]
AKIKI 2015	154	311	147	308	18.3%	1.04 [0.88 , 1.22]
STARRT-AKI 2019	729	1465	766	1462	23.6%	0.95 [0.88 , 1.02]
Subtotal (95% CI)		**2374**		**2343**	**100.0%**	**1.07 [0.94 , 1.22]**
Total events:	1170		1154			
Heterogeneity: Tau² = 0.02; Chi² = 20.10, df = 9 (P = 0.02); I² = 55%						
Test for overall effect: Z = 1.03 (P = 0.30)						
1.3.2 Survivors free from KRT according to ITT after 30 days						
Xia 2019	13	15	5	17	0.4%	2.95 [1.37 , 6.32]
EARLYRRT 2018	9	10	5	11	0.5%	1.98 [1.00 , 3.91]
Sugahara 2004	10	12	2	2	0.7%	0.97 [0.55 , 1.72]
FST 2018	21	22	19	25	3.7%	1.26 [0.99 , 1.59]
ELAIN 2016	60	67	46	53	8.8%	1.03 [0.90 , 1.18]
STARRT-AKI Pilot 2013	30	30	31	33	11.5%	1.06 [0.96 , 1.18]
Bouman 2002	38	39	22	22	13.7%	0.98 [0.90 , 1.07]
AKIKI 2015	154	157	147	155	19.6%	1.03 [0.99 , 1.08]
IDEAL-ICU 2014	99	101	107	110	19.8%	1.01 [0.97 , 1.05]
STARRT-AKI 2019	729	814	766	815	21.2%	0.95 [0.93 , 0.98]
Subtotal (95% CI)		**1267**		**1243**	**100.0%**	**1.02 [0.97 , 1.07]**
Total events:	1163		1150			
Heterogeneity: Tau² = 0.00; Chi² = 29.08, df = 9 (P = 0.0006); I² = 69%						
Test for overall effect: Z = 0.85 (P = 0.40)						



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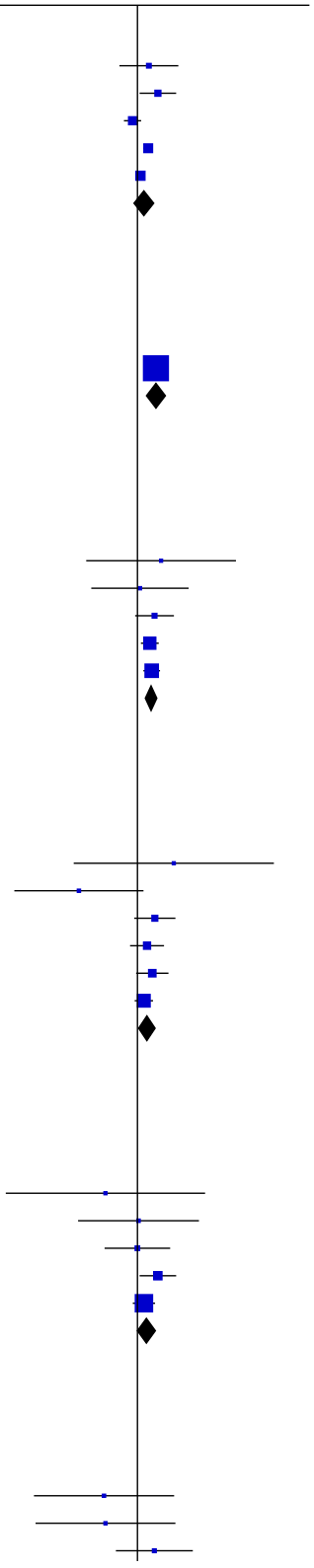
Analysis 1.4. Comparison 1: Early versus standard initiation, Outcome 4: Adverse events

Study or Subgroup	Early initiation Events	Total	Standard initiation Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 Any adverse event						
Bouman 2002	14	70	5	36	8.0%	1.44 [0.56 , 3.68]
AKIKI 2015	31	311	16	308	14.3%	1.92 [1.07 , 3.44]
STARRT-AKI Pilot 2013	30	48	38	52	23.2%	0.86 [0.65 , 1.13]
STARRT-AKI 2019	346	1465	245	1462	26.6%	1.41 [1.22 , 1.63]
ELAIN 2016	112	112	108	119	27.9%	1.10 [1.04 , 1.17]
Subtotal (95% CI)		**2006**		**1977**	**100.0%**	**1.23 [0.90 , 1.68]**
Total events:	533		412			
Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 42.13$, df = 4 (P < 0.00001); $I^2 = 91\%$						
Test for overall effect: Z = 1.27 (P = 0.20)						
1.4.2 Hypophosphataemia						
STARRT-AKI 2019	112	1465	62	1462	100.0%	1.80 [1.33 , 2.44]
Subtotal (95% CI)		**1465**		**1462**	**100.0%**	**1.80 [1.33 , 2.44]**
Total events:	112		62			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.83 (P = 0.0001)						
1.4.3 Hypotension						
ELAIN 2016	2	112	1	119	0.6%	2.13 [0.20 , 23.11]
STARRT-AKI Pilot 2013	3	48	3	52	1.4%	1.08 [0.23 , 5.11]
FST 2018	20	58	12	60	8.8%	1.72 [0.93 , 3.20]
IDEAL-ICU 2014	86	246	57	242	41.6%	1.48 [1.12 , 1.97]
STARRT-AKI 2019	131	1465	83	1462	47.6%	1.58 [1.21 , 2.05]
Subtotal (95% CI)		**1929**		**1935**	**100.0%**	**1.54 [1.29 , 1.85]**
Total events:	242		156			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.49$, df = 4 (P = 0.97); $I^2 = 0\%$						
Test for overall effect: Z = 4.65 (P < 0.00001)						
1.4.4 Cardiac-rhythm disorder						
ELAIN 2016	1	112	0	119	0.7%	3.19 [0.13 , 77.40]
STARRT-AKI Pilot 2013	1	48	7	52	1.6%	0.15 [0.02 , 1.21]
IDEAL-ICU 2014	23	246	13	242	13.7%	1.74 [0.90 , 3.36]
FST 2018	21	58	16	60	19.0%	1.36 [0.79 , 2.33]
STARRT-AKI 2019	37	1465	23	1462	20.5%	1.61 [0.96 , 2.69]
AKIKI 2015	78	311	63	308	44.5%	1.23 [0.92 , 1.64]
Subtotal (95% CI)		**2240**		**2243**	**100.0%**	**1.35 [1.04 , 1.75]**
Total events:	161		122			
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 5.95$, df = 5 (P = 0.31); $I^2 = 16\%$						
Test for overall effect: Z = 2.24 (P = 0.02)						
1.4.5 Infection						
STARRT-AKI Pilot 2013	0	48	1	52	0.8%	0.36 [0.02 , 8.64]
FST 2018	2	58	2	60	2.2%	1.03 [0.15 , 7.10]
STARRT-AKI 2019	7	1465	7	1462	7.5%	1.00 [0.35 , 2.84]
AKIKI 2015	31	311	16	308	24.2%	1.92 [1.07 , 3.44]
IDEAL-ICU 2014	55	246	44	242	65.3%	1.23 [0.86 , 1.75]
Subtotal (95% CI)		**2128**		**2124**	**100.0%**	**1.33 [1.00 , 1.77]**
Total events:	95		70			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.72$, df = 4 (P = 0.61); $I^2 = 0\%$						
Test for overall effect: Z = 1.95 (P = 0.05)						
1.4.6 Bleeding						
FST 2018	1	58	3	60	1.3%	0.34 [0.04 , 3.22]
STARRT-AKI Pilot 2013	1	48	3	52	1.3%	0.36 [0.04 , 3.35]
Bouman 2002	10	70	3	36	4.3%	1.71 [0.50 , 5.84]



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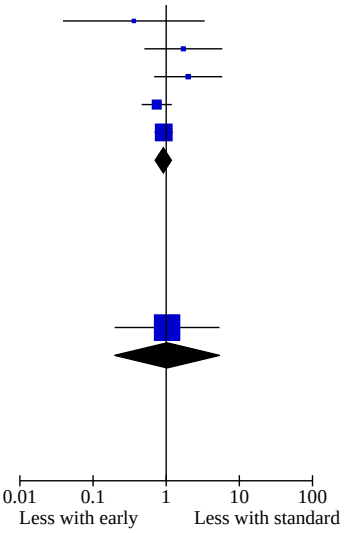
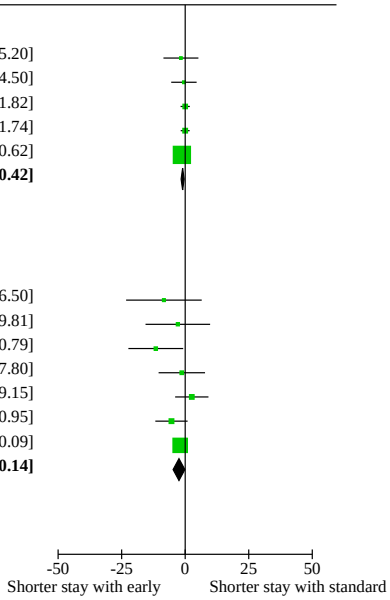
Analysis 1.4. (Continued)

STARRT-AKI Pilot 2013	1	48	3	52	1.3%	0.36 [0.04 , 3.35]
Bouman 2002	10	70	3	36	4.3%	1.71 [0.50 , 5.84]
STARRT-AKI 2019	10	1465	5	1462	5.5%	2.00 [0.68 , 5.83]
AKIKI 2015	27	311	36	308	26.4%	0.74 [0.46 , 1.19]
IDEAL-ICU 2014	64	246	68	242	61.2%	0.93 [0.69 , 1.24]
Subtotal (95% CI)		**2198**		**2160**	**100.0%**	**0.91 [0.71 , 1.18]**
Total events:	113		118			
Heterogeneity: Tau² = 0.01; Chi² = 5.20, df = 5 (P = 0.39); I² = 4%						
Test for overall effect: Z = 0.70 (P = 0.48)						
1.4.7 Thrombocytopenia						
Bouman 2002	4	70	2	36	100.0%	1.03 [0.20 , 5.35]
Subtotal (95% CI)		**70**		**36**	**100.0%**	**1.03 [0.20 , 5.35]**
Total events:	4		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.03 (P = 0.97)						



Analysis 1.5. Comparison 1: Early versus standard initiation, Outcome 5: Length of stay

	Early initiation			Standard initiation				Mean Difference	Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**	**IV, Random, 95% CI**
1.5.1 Length of stay in ICU									
STARRT-AKI Pilot 2013	16.17	16.59	48	17.85	18.49	52	0.7%	-1.68 [-8.56 , 5.20]	
Bouman 2002	13	12.5	70	13.5	12.4	36	1.4%	-0.50 [-5.50 , 4.50]	
AKIKI 2015	13	11.18	311	13	11.9	308	10.5%	0.00 [-1.82 , 1.82]	
IDEAL-ICU 2014	13.71	9.9	246	13.72	9.87	242	11.3%	-0.01 [-1.76 , 1.74]	
STARRT-AKI 2019	10.05	8.18	1465	11.35	10.4	1462	76.0%	-1.30 [-1.98 , -0.62]	
Subtotal (95% CI)			**2140**			**2100**	**100.0%**	**-1.01 [-1.60 , -0.42]**	
Heterogeneity: Tau² = 0.00; Chi² = 3.21, df = 4 (P = 0.52); I² = 0%									
Test for overall effect: Z = 3.34 (P = 0.0008)									
1.5.2 Length of stay in hospital									
Bouman 2002	28.33	27	70	36.7	41.2	36	2.4%	-8.37 [-23.24 , 6.50]	
FST 2018	29.7	35.5	58	32.6	34.9	60	3.2%	-2.90 [-15.61 , 9.81]	
ELAIN 2016	36.33	36.3	112	47.9	46.9	119	4.4%	-11.57 [-22.35 , -0.79]	
STARRT-AKI Pilot 2013	32.67	22.5	48	34	24.1	52	6.0%	-1.33 [-10.46 , 7.80]	
AKIKI 2015	31	46.9	311	28.4	35.5	308	11.1%	2.60 [-3.95 , 9.15]	
IDEAL-ICU 2014	29.3	29.1	246	34.7	41.3	242	11.7%	-5.40 [-11.75 , 0.95]	
STARRT-AKI 2019	31.33	25.24	1465	33.33	27.47	1462	61.2%	-2.00 [-3.91 , -0.09]	
Subtotal (95% CI)			**2310**			**2279**	**100.0%**	**-2.45 [-4.75 , -0.14]**	
Heterogeneity: Tau² = 1.31; Chi² = 6.69, df = 6 (P = 0.35); I² = 10%									
Test for overall effect: Z = 2.08 (P = 0.04)									
Test for subgroup differences: Chi² = 1.40, df = 1 (P = 0.24), I² = 28.7%									



Comparison 2. Subgroup analysis: death

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Death by AKI aetiology	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1.1 Patients with AKI related to non-surgical causes	9	4461	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.94, 1.09]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1.2 Patients with AKI related to surgical causes	3	365	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.31, 1.36]
2.2 Death by KRT initiation	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.2.1 Initiation according KDIGO stage 2	3	3258	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.78, 1.15]
2.2.2 Initiation according to KDIGO3, AKI RIFLE-F stage and AKIN3	4	1216	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.79, 1.15]
2.2.3 Initiation according other criteria	3	218	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.86, 1.38]
2.3 Death by KRT modality	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.3.1 Continuous KRT	8	692	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.65, 1.14]
2.3.2 Continuous and intermittent KRT	4	4134	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.94, 1.10]
2.4 Death by illness severity score	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.4.1 Sequential Organ Failure Assessment (SOFA) score > 12	3	819	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.75, 1.20]
2.4.2 Sequential Organ Failure Assessment (SOFA) score ≤ 12	6	3870	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.94, 1.10]

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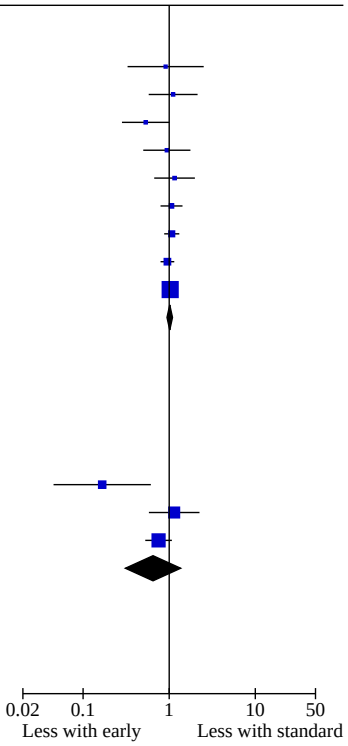
Analysis 2.1. Comparison 2: Subgroup analysis: death, Outcome 1: Death by AKI aetiology

Study or Subgroup	Early initiation Events	Total	Standard initiation Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 Patients with AKI related to non-surgical causes						
Yin 2018	6	33	6	30	0.5%	0.91 [0.33 , 2.52]
EARLYRRT 2018	10	20	9	20	1.3%	1.11 [0.58 , 2.14]
Tang 2016	8	23	15	23	1.3%	0.53 [0.28 , 1.01]
STARRT-AKI Pilot 2013	13	48	15	52	1.4%	0.94 [0.50 , 1.76]
Xia 2019	15	30	13	30	1.8%	1.15 [0.67 , 1.99]
FST 2018	36	58	35	60	6.2%	1.06 [0.79 , 1.43]
IDEAL-ICU 2014	111	246	102	242	13.2%	1.07 [0.87 , 1.31]
AKIKI 2015	129	311	134	308	16.0%	0.95 [0.79 , 1.15]
STARRT-AKI 2019	538	1465	523	1462	58.3%	1.03 [0.93 , 1.13]
Subtotal (95% CI)		**2234**		**2227**	**100.0%**	**1.01 [0.94 , 1.09]**
Total events:	866		852			
Heterogeneity: Tau² = 0.00; Chi² = 5.21, df = 8 (P = 0.73); I² = 0%						
Test for overall effect: Z = 0.39 (P = 0.69)						
2.1.2 Patients with AKI related to surgical causes						
Sugahara 2004	2	14	12	14	19.6%	0.17 [0.05 , 0.61]
Bouman 2002	20	70	9	36	35.4%	1.14 [0.58 , 2.25]
ELAIN 2016	34	112	48	119	45.0%	0.75 [0.53 , 1.07]
Subtotal (95% CI)		**196**		**169**	**100.0%**	**0.65 [0.31 , 1.36]**
Total events:	56		69			
Heterogeneity: Tau² = 0.28; Chi² = 6.72, df = 2 (P = 0.03); I² = 70%						
Test for overall effect: Z = 1.15 (P = 0.25)						
Test for subgroup differences: Chi² = 1.40, df = 1 (P = 0.24), I² = 28.3%						



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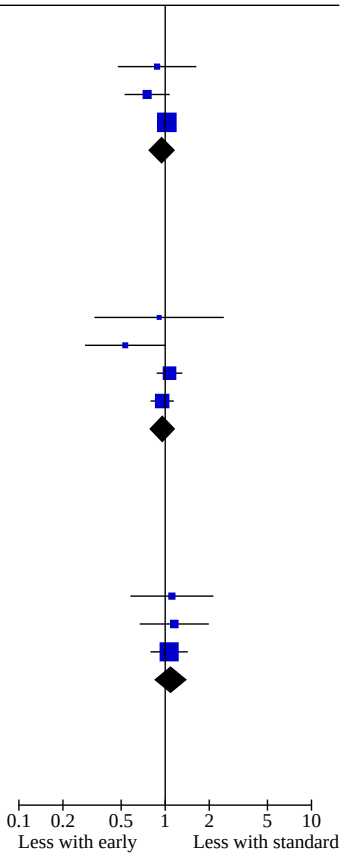
Analysis 2.2. Comparison 2: Subgroup analysis: death, Outcome 2: Death by KRT initiation

Study or Subgroup	Early initiation Events	Total	Standard initiation Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 Initiation according KDIGO stage 2						
STARRT-AKI Pilot 2013	13	48	16	52	8.9%	0.88 [0.47 , 1.63]
ELAIN 2016	34	112	48	119	22.1%	0.75 [0.53 , 1.07]
STARRT-AKI 2019	538	1465	523	1462	68.9%	1.03 [0.93 , 1.13]
Subtotal (95% CI)		**1625**		**1633**	**100.0%**	**0.95 [0.78 , 1.15]**
Total events:	585		587			
Heterogeneity: Tau² = 0.01; Chi² = 2.90, df = 2 (P = 0.23); I² = 31%						
Test for overall effect: Z = 0.56 (P = 0.57)						
2.2.2 Initiation according to KDIGO3, AKI RIFLE-F stage and AKIN3						
Yin 2018	6	33	6	30	3.3%	0.91 [0.33 , 2.52]
Tang 2016	8	23	15	23	8.0%	0.53 [0.28 , 1.01]
IDEAL-ICU 2014	111	246	102	242	42.4%	1.07 [0.87 , 1.31]
AKIKI 2015	129	311	134	308	46.3%	0.95 [0.79 , 1.15]
Subtotal (95% CI)		**613**		**603**	**100.0%**	**0.95 [0.79 , 1.15]**
Total events:	254		257			
Heterogeneity: Tau² = 0.01; Chi² = 4.37, df = 3 (P = 0.22); I² = 31%						
Test for overall effect: Z = 0.48 (P = 0.63)						
2.2.3 Initiation according other criteria						
EARLYRRT 2018	10	20	9	20	13.5%	1.11 [0.58 , 2.14]
Xia 2019	15	30	13	30	19.5%	1.15 [0.67 , 1.99]
FST 2018	36	58	35	60	66.9%	1.06 [0.79 , 1.43]
Subtotal (95% CI)		**108**		**110**	**100.0%**	**1.09 [0.86 , 1.38]**
Total events:	61		57			
Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 2 (P = 0.96); I² = 0%						
Test for overall effect: Z = 0.68 (P = 0.49)						
Test for subgroup differences: Chi² = 0.92, df = 2 (P = 0.63), I² = 0%						



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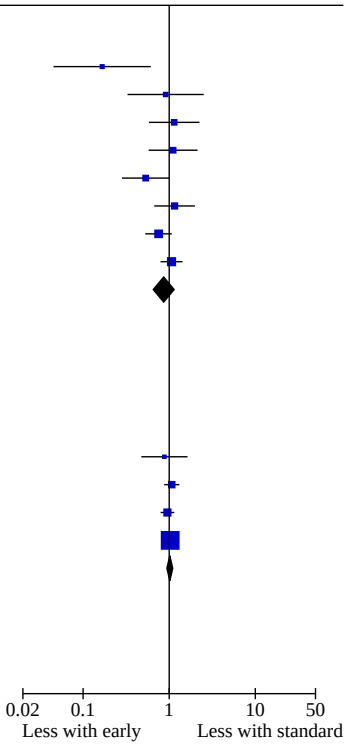
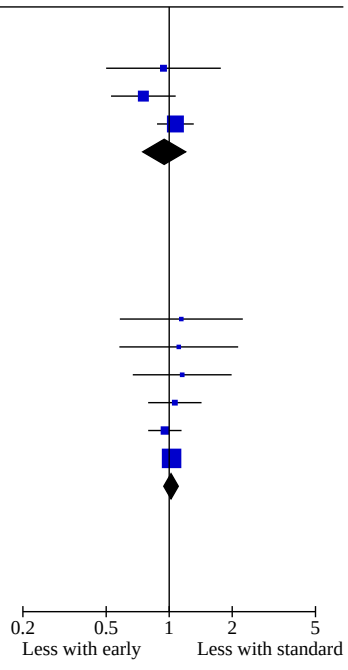
Analysis 2.3. Comparison 2: Subgroup analysis: death, Outcome 3: Death by KRT modality

Study or Subgroup	Early initiation Events	Total	Standard initiation Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.3.1 Continuous KRT						
Sugahara 2004	2	14	12	14	4.0%	0.17 [0.05 , 0.61]
Yin 2018	6	33	6	30	6.0%	0.91 [0.33 , 2.52]
Bouman 2002	20	70	9	36	10.8%	1.14 [0.58 , 2.25]
EARLYRRT 2018	10	20	9	20	11.3%	1.11 [0.58 , 2.14]
Tang 2016	8	23	15	23	11.7%	0.53 [0.28 , 1.01]
Xia 2019	15	30	13	30	13.9%	1.15 [0.67 , 1.99]
ELAIN 2016	34	112	48	119	20.0%	0.75 [0.53 , 1.07]
FST 2018	36	58	35	60	22.3%	1.06 [0.79 , 1.43]
Subtotal (95% CI)		**360**		**332**	**100.0%**	**0.86 [0.65 , 1.14]**
Total events:	131		147			
Heterogeneity: Tau² = 0.07; Chi² = 13.41, df = 7 (P = 0.06); I² = 48%						
Test for overall effect: Z = 1.03 (P = 0.30)						
2.3.2 Continuous and intermittent KRT						
STARRT-AKI Pilot 2013	13	48	16	52	1.6%	0.88 [0.47 , 1.63]
IDEAL-ICU 2014	111	246	102	242	14.8%	1.07 [0.87 , 1.31]
AKIKI 2015	129	311	134	308	18.0%	0.95 [0.79 , 1.15]
STARRT-AKI 2019	538	1465	523	1462	65.6%	1.03 [0.93 , 1.13]
Subtotal (95% CI)		**2070**		**2064**	**100.0%**	**1.02 [0.94 , 1.10]**
Total events:	791		775			
Heterogeneity: Tau² = 0.00; Chi² = 0.97, df = 3 (P = 0.81); I² = 0%						
Test for overall effect: Z = 0.42 (P = 0.67)						
Test for subgroup differences: Chi² = 1.23, df = 1 (P = 0.27), I² = 18.8%						



Analysis 2.4. Comparison 2: Subgroup analysis: death, Outcome 4: Death by illness severity score

Study or Subgroup	Early initiation Events	Total	Standard initiation Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.4.1 Sequential Organ Failure Assessment (SOFA) score > 12						
STARRT-AKI Pilot 2013	13	48	15	52	12.2%	0.94 [0.50 , 1.76]
ELAIN 2016	34	112	48	119	30.4%	0.75 [0.53 , 1.07]
IDEAL-ICU 2014	111	246	102	242	57.3%	1.07 [0.87 , 1.31]
Subtotal (95% CI)		**406**		**413**	**100.0%**	**0.95 [0.75 , 1.20]**
Total events:	158		165			
Heterogeneity: Tau² = 0.01; Chi² = 2.89, df = 2 (P = 0.24); I² = 31%						
Test for overall effect: Z = 0.46 (P = 0.65)						
2.4.2 Sequential Organ Failure Assessment (SOFA) score ≤ 12						
Bouman 2002	20	70	9	36	1.4%	1.14 [0.58 , 2.25]
EARLYRRT 2018	10	20	9	20	1.5%	1.11 [0.58 , 2.14]
Xia 2019	15	30	13	30	2.1%	1.15 [0.67 , 1.99]
FST 2018	36	58	35	60	7.4%	1.06 [0.79 , 1.43]
AKIKI 2015	129	311	134	308	18.9%	0.95 [0.79 , 1.15]
STARRT-AKI 2019	538	1465	523	1462	68.7%	1.03 [0.93 , 1.13]
Subtotal (95% CI)		**1954**		**1916**	**100.0%**	**1.02 [0.94 , 1.10]**
Total events:	748		723			
Heterogeneity: Tau² = 0.00; Chi² = 0.99, df = 5 (P = 0.96); I² = 0%						
Test for overall effect: Z = 0.49 (P = 0.62)						
Test for subgroup differences: Chi² = 0.35, df = 1 (P = 0.55), I² = 0%						



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Comparison 3. Subgroup analysis: death or non-recovery of kidney function at day 90

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 AKI aetiology	6	4011	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.74, 1.11]
3.1.1 Non-surgical causes	3	3646	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.97, 1.11]
3.1.2 Surgical causes	3	365	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.33, 1.33]
3.2 AKI criteria	6	4011	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.74, 1.11]
3.2.1 KDIGO stage 2	1	619	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.79, 1.15]
3.2.2 KDIGO stage 3/RIFLE-F AKIN	3	3258	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.70, 1.19]
3.2.3 Other criteria	2	134	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.07, 3.21]
3.3 KRT modality	6	4011	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.74, 1.11]
3.3.1 Continuous KRT	3	365	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.33, 1.33]
3.3.2 Continuous and intermittent KRT	3	3646	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.97, 1.11]
3.4 Illness severity score	5	3983	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.83, 1.10]
3.4.1 Sequential Organ Failure Assessment (SOFA) score > 12	2	331	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.62, 0.97]
3.4.2 Sequential Organ Failure Assessment (SOFA) score ≤ 12	3	3652	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.97, 1.12]

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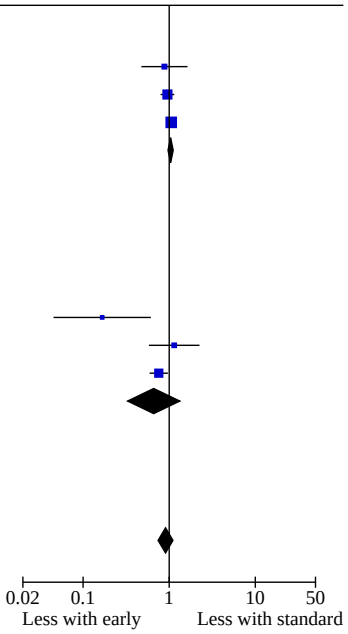
Analysis 3.1. Comparison 3: Subgroup analysis: death or non-recovery of kidney function at day 90, Outcome 1: AKI aetiology

Study or Subgroup	Early initiation Events	Total	Standard initiation Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 Non-surgical causes						
STARRT-AKI Pilot 2013	13	48	16	52	8.0%	0.88 [0.47 , 1.63]
AKIKI 2015	129	311	134	308	26.9%	0.95 [0.79 , 1.15]
STARRT-AKI 2019	728	1465	688	1462	33.3%	1.06 [0.98 , 1.14]
Subtotal (95% CI)		**1824**		**1822**	**68.1%**	**1.04 [0.97 , 1.11]**
Total events:	870		838			
Heterogeneity: Tau² = 0.00; Chi² = 1.30, df = 2 (P = 0.52); I² = 0%						
Test for overall effect: Z = 1.07 (P = 0.28)						
3.1.2 Surgical causes						
Sugahara 2004	2	14	12	14	2.2%	0.17 [0.05 , 0.61]
Bouman 2002	20	70	9	36	6.9%	1.14 [0.58 , 2.25]
ELAIN 2016	52	112	73	119	22.8%	0.76 [0.59 , 0.97]
Subtotal (95% CI)		**196**		**169**	**31.9%**	**0.66 [0.33 , 1.33]**
Total events:	74		94			
Heterogeneity: Tau² = 0.25; Chi² = 6.72, df = 2 (P = 0.03); I² = 70%						
Test for overall effect: Z = 1.17 (P = 0.24)						
Total (95% CI)		**2020**		**1991**	**100.0%**	**0.91 [0.74 , 1.11]**
Total events:	944		932			
Heterogeneity: Tau² = 0.03; Chi² = 14.79, df = 5 (P = 0.01); I² = 66%						
Test for overall effect: Z = 0.97 (P = 0.33)						
Test for subgroup differences: Chi² = 1.60, df = 1 (P = 0.21), I² = 37.5%						



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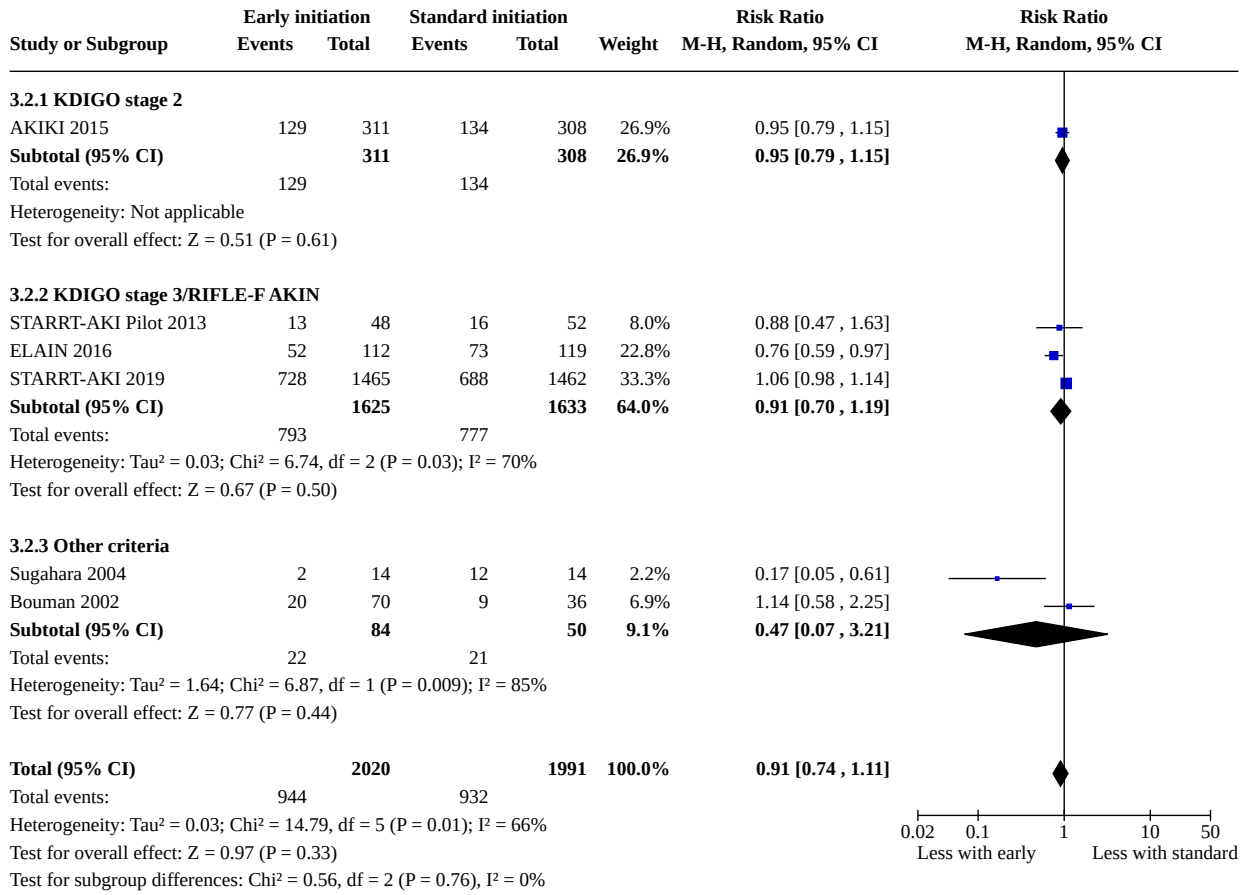
Analysis 3.2. Comparison 3: Subgroup analysis: death or non-recovery of kidney function at day 90, Outcome 2: AKI criteria



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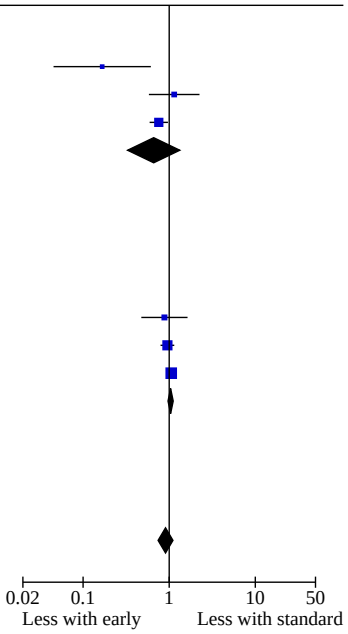
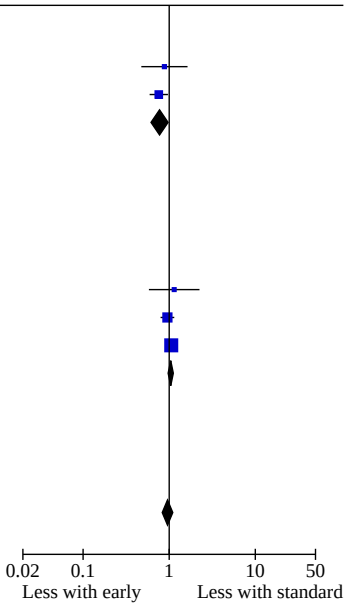
Analysis 3.3. Comparison 3: Subgroup analysis: death or non-recovery of kidney function at day 90, Outcome 3: KRT modality

Study or Subgroup	Early initiation Events	Total	Standard initiation Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.3.1 Continuous KRT						
Sugahara 2004	2	14	12	14	2.2%	0.17 [0.05 , 0.61]
Bouman 2002	20	70	9	36	6.9%	1.14 [0.58 , 2.25]
ELAIN 2016	52	112	73	119	22.8%	0.76 [0.59 , 0.97]
Subtotal (95% CI)		**196**		**169**	**31.9%**	**0.66 [0.33 , 1.33]**
Total events:	74		94			
Heterogeneity: Tau² = 0.25; Chi² = 6.72, df = 2 (P = 0.03); I² = 70%						
Test for overall effect: Z = 1.17 (P = 0.24)						
3.3.2 Continuous and intermittent KRT						
STARRT-AKI Pilot 2013	13	48	16	52	8.0%	0.88 [0.47 , 1.63]
AKIKI 2015	129	311	134	308	26.9%	0.95 [0.79 , 1.15]
STARRT-AKI 2019	728	1465	688	1462	33.3%	1.06 [0.98 , 1.14]
Subtotal (95% CI)		**1824**		**1822**	**68.1%**	**1.04 [0.97 , 1.11]**
Total events:	870		838			
Heterogeneity: Tau² = 0.00; Chi² = 1.30, df = 2 (P = 0.52); I² = 0%						
Test for overall effect: Z = 1.07 (P = 0.28)						
Total (95% CI)		**2020**		**1991**	**100.0%**	**0.91 [0.74 , 1.11]**
Total events:	944		932			
Heterogeneity: Tau² = 0.03; Chi² = 14.79, df = 5 (P = 0.01); I² = 66%						
Test for overall effect: Z = 0.97 (P = 0.33)						
Test for subgroup differences: Chi² = 1.60, df = 1 (P = 0.21), I² = 37.5%						



Analysis 3.4. Comparison 3: Subgroup analysis: death or non-recovery of kidney function at day 90, Outcome 4: Illness severity score

Study or Subgroup	Early initiation Events	Total	Standard initiation Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.4.1 Sequential Organ Failure Assessment (SOFA) score > 12						
STARRT-AKI Pilot 2013	13	48	16	52	4.7%	0.88 [0.47 , 1.63]
ELAIN 2016	52	112	73	119	20.0%	0.76 [0.59 , 0.97]
Subtotal (95% CI)		**160**		**171**	**24.7%**	**0.77 [0.62 , 0.97]**
Total events:	65		89			
Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 1 (P = 0.65); I² = 0%						
Test for overall effect: Z = 2.22 (P = 0.03)						
3.4.2 Sequential Organ Failure Assessment (SOFA) score ≤ 12						
Bouman 2002	20	70	9	36	4.0%	1.14 [0.58 , 2.25]
AKIKI 2015	129	311	134	308	27.2%	0.95 [0.79 , 1.15]
STARRT-AKI 2019	728	1465	688	1462	44.2%	1.06 [0.98 , 1.14]
Subtotal (95% CI)		**1846**		**1806**	**75.3%**	**1.04 [0.97 , 1.12]**
Total events:	877		831			
Heterogeneity: Tau² = 0.00; Chi² = 1.10, df = 2 (P = 0.58); I² = 0%						
Test for overall effect: Z = 1.16 (P = 0.25)						
Total (95% CI)		**2006**		**1977**	**100.0%**	**0.96 [0.83 , 1.10]**
Total events:	942		920			
Heterogeneity: Tau² = 0.01; Chi² = 7.36, df = 4 (P = 0.12); I² = 46%						
Test for overall effect: Z = 0.63 (P = 0.53)						
Test for subgroup differences: Chi² = 6.07, df = 1 (P = 0.01), I² = 83.5%						



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Comparison 4. Subgroup analysis: recovery of kidney function

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Recovery of kidney function by AKI aetiology	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1.1 AKI related to non-surgical causes	7	4352	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.91, 1.11]
4.1.2 AKI related to surgical causes	3	365	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.78, 2.38]
4.2 Recovery of kidney function by definition of early KRT Initiation	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.2.1 Initiation according KDIGO stage 2	3	3258	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.86, 1.36]
4.2.2 Initiation according KDIGO stage 3/RIFLE-F AKIN	2	1107	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.88, 1.13]
4.2.3 Initiation according to other criteria	3	218	Risk Ratio (M-H, Random, 95% CI)	1.55 [0.95, 2.53]
4.3 Recovery of kidney function by KRT modality	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.3.1 Continuous KRT	6	583	Risk Ratio (M-H, Random, 95% CI)	1.42 [0.99, 2.03]
4.3.2 Continuous and intermittent KRT	4	4134	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.91, 1.02]

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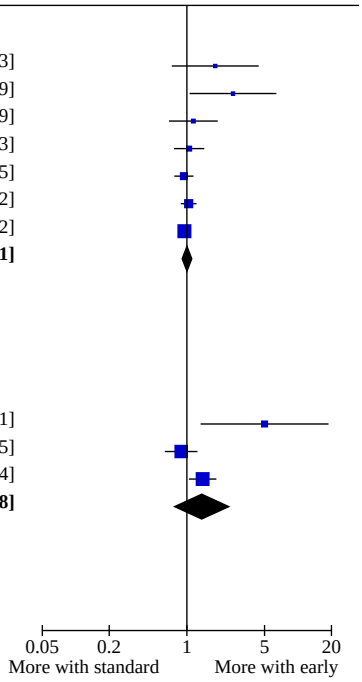
Analysis 4.1. Comparison 4: Subgroup analysis: recovery of kidney function, Outcome 1: Recovery of kidney function by AKI aetiology

Study or Subgroup	More with standard Events	Total	Standard initiation Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
4.1.1 AKI related to non-surgical causes						
EARLYRRT 2018	9	20	5	20	1.2%	1.80 [0.73 , 4.43]
Xia 2019	13	30	5	30	1.2%	2.60 [1.06 , 6.39]
FST 2018	21	58	19	60	3.6%	1.14 [0.69 , 1.89]
STARRT-AKI Pilot 2013	30	48	31	52	8.6%	1.05 [0.77 , 1.43]
IDEAL-ICU 2014	106	246	111	242	17.6%	0.94 [0.77 , 1.15]
AKIKI 2015	154	311	147	308	22.9%	1.04 [0.88 , 1.22]
STARRT-AKI 2019	729	1465	766	1462	44.9%	0.95 [0.88 , 1.02]
Subtotal (95% CI)		**2178**		**2174**	**100.0%**	**1.00 [0.91 , 1.11]**
Total events:	1062		1084			
Heterogeneity: Tau² = 0.00; Chi² = 8.19, df = 6 (P = 0.22); I² = 27%						
Test for overall effect: Z = 0.03 (P = 0.97)						
4.1.2 AKI related to surgical causes						
Sugahara 2004	10	14	2	14	13.2%	5.00 [1.33 , 18.81]
Bouman 2002	38	70	22	36	42.4%	0.89 [0.63 , 1.25]
ELAIN 2016	60	112	46	119	44.4%	1.39 [1.04 , 1.84]
Subtotal (95% CI)		**196**		**169**	**100.0%**	**1.36 [0.78 , 2.38]**
Total events:	108		70			
Heterogeneity: Tau² = 0.16; Chi² = 8.95, df = 2 (P = 0.01); I² = 78%						
Test for overall effect: Z = 1.07 (P = 0.28)						
Test for subgroup differences: Chi² = 1.10, df = 1 (P = 0.29), I² = 9.4%						



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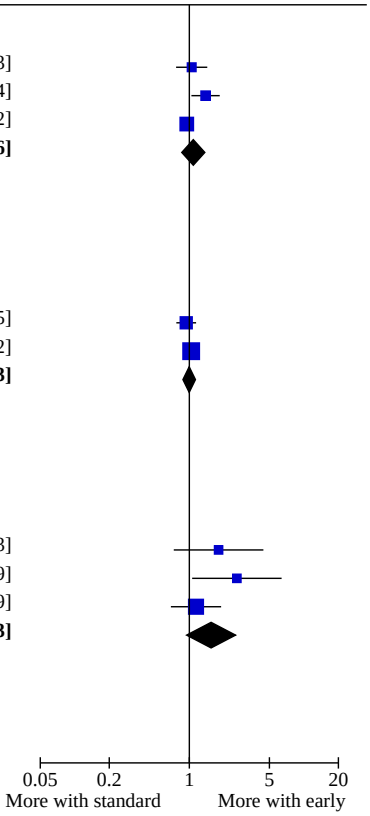
Analysis 4.2. Comparison 4: Subgroup analysis: recovery of kidney function, Outcome 2: Recovery of kidney function by definition of early KRT Initiation

Study or Subgroup	Early initiation Events	Total	Standard initiation Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
4.2.1 Initiation according KDIGO stage 2						
STARRT-AKI Pilot 2013	30	48	31	52	25.7%	1.05 [0.77 , 1.43]
ELAIN 2016	60	112	46	119	28.0%	1.39 [1.04 , 1.84]
STARRT-AKI 2019	729	1465	766	1462	46.3%	0.95 [0.88 , 1.02]
Subtotal (95% CI)		**1625**		**1633**	**100.0%**	**1.08 [0.86 , 1.36]**
Total events:	819		843			
Heterogeneity: Tau² = 0.03; Chi² = 6.60, df = 2 (P = 0.04); I² = 70%						
Test for overall effect: Z = 0.67 (P = 0.50)						
4.2.2 Initiation according KDIGO stage 3/RIFLE-F AKIN						
IDEAL-ICU 2014	106	246	111	242	40.0%	0.94 [0.77 , 1.15]
AKIKI 2015	154	311	147	308	60.0%	1.04 [0.88 , 1.22]
Subtotal (95% CI)		**557**		**550**	**100.0%**	**1.00 [0.88 , 1.13]**
Total events:	260		258			
Heterogeneity: Tau² = 0.00; Chi² = 0.58, df = 1 (P = 0.45); I² = 0%						
Test for overall effect: Z = 0.05 (P = 0.96)						
4.2.3 Initiation according to other criteria						
EARLYRRT 2018	9	20	5	20	23.7%	1.80 [0.73 , 4.43]
Xia 2019	13	30	5	30	23.8%	2.60 [1.06 , 6.39]
FST 2018	21	58	19	60	52.5%	1.14 [0.69 , 1.89]
Subtotal (95% CI)		**108**		**110**	**100.0%**	**1.55 [0.95 , 2.53]**
Total events:	43		29			
Heterogeneity: Tau² = 0.05; Chi² = 2.72, df = 2 (P = 0.26); I² = 26%						
Test for overall effect: Z = 1.75 (P = 0.08)						
Test for subgroup differences: Chi² = 3.07, df = 2 (P = 0.22), I² = 34.9%						



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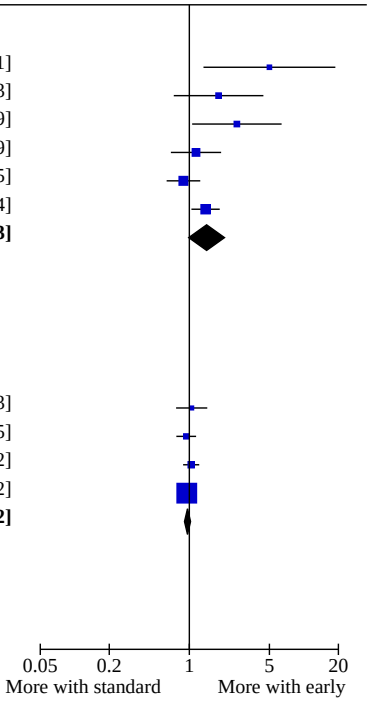
Analysis 4.3. Comparison 4: Subgroup analysis: recovery of kidney function, Outcome 3: Recovery of kidney function by KRT modality

Study or Subgroup	Early initiation Events	Total	Standard initiation Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
4.3.1 Continuous KRT						
Sugahara 2004	10	14	2	14	6.0%	5.00 [1.33 , 18.81]
EARLYRRT 2018	9	20	5	20	10.7%	1.80 [0.73 , 4.43]
Xia 2019	13	30	5	30	10.7%	2.60 [1.06 , 6.39]
FST 2018	21	58	19	60	19.9%	1.14 [0.69 , 1.89]
Bouman 2002	38	70	22	36	25.4%	0.89 [0.63 , 1.25]
ELAIN 2016	60	112	46	119	27.2%	1.39 [1.04 , 1.84]
Subtotal (95% CI)		**304**		**279**	**100.0%**	**1.42 [0.99 , 2.03]**
Total events:	151		99			
Heterogeneity: Tau² = 0.10; Chi² = 12.54, df = 5 (P = 0.03); I² = 60%						
Test for overall effect: Z = 1.90 (P = 0.06)						
4.3.2 Continuous and intermittent KRT						
STARRT-AKI Pilot 2013	30	48	31	52	3.7%	1.05 [0.77 , 1.43]
IDEAL-ICU 2014	106	246	111	242	9.3%	0.94 [0.77 , 1.15]
AKIKI 2015	154	311	147	308	14.0%	1.04 [0.88 , 1.22]
STARRT-AKI 2019	729	1465	766	1462	72.9%	0.95 [0.88 , 1.02]
Subtotal (95% CI)		**2070**		**2064**	**100.0%**	**0.96 [0.91 , 1.02]**
Total events:	1019		1055			
Heterogeneity: Tau² = 0.00; Chi² = 1.30, df = 3 (P = 0.73); I² = 0%						
Test for overall effect: Z = 1.18 (P = 0.24)						
Test for subgroup differences: Chi² = 4.27, df = 1 (P = 0.04), I² = 76.6%						



APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. MeSH descriptor: [Acute Kidney Injury] explode all trees 2. "acute kidney failure":ti,ab,kw OR "acute renal failure":ti,ab,kw in Trials 3. "acute kidney injury":ti,ab,kw OR "acute renal injury":ti,ab,kw in Trials 4. "acute kidney insufficiency":ti,ab,kw OR "acute renal insufficiency":ti,ab,kw in Trials 5. "acute tubular necrosis":ti in Trials 6. (ARI or AKI or ARF or AKF or ATN):ti,ab,kw in Trials 7. #1 or #2 or #3 or #4 or #5 or #6 in Trials 8. MeSH descriptor: [Renal Replacement Therapy] this term only 9. MeSH descriptor: [Renal Dialysis] explode all trees 10.continuous near/2 haemofiltration:ti,ab,kw in Trials 11.continuous near/2 haemodiafiltration:ti,ab,kw in Trials 12.continuous near/2 haemodialysis:ti,ab,kw in Trials 13.continuous near/2 haemodialysis:ti,ab,kw in Trials 14.continuous next ultrafiltration:ti,ab,kw in Trials 15.continuous near/2 haemofiltration:ti,ab,kw in Trials 16.CVVH or CVVHDF or CVVHD or SCUF or CRRT:ti,ab,kw in Trials 17.renal replacement therap*:ti,ab,kw in Trials

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(Continued)

	18.intermittent hemodialysis or intermittent haemodialysis:ti,ab,kw (Word variations have been searched) 19."sustained low efficiency dialysis" or SLED:ti,ab,kw (Word variations have been searched) 20."extended daily dialysis" or EDD:ti,ab,kw (Word variations have been searched) 21.hemoperfusion:ti,ab,kw (Word variations have been searched) 22.{or #8-#21} 23.{and #7, #22}
MEDLINE	1. exp Acute Kidney Injury/ 2. (acute kidney failure or acute renal failure).tw. 3. (acute kidney injur$ or acute renal injur$).tw. 4. (acute kidney insufficie$ or acute renal insufficie$).tw. 5. acute tubular necrosis.tw. 6. (ARI or AKI or ARF or AKF or ATN).tw. 7. or/1-6 8. Renal Replacement Therapy/ 9. exp Renal Dialysis/ 10.(continuous adj3 hemofiltration).tw. 11.(continuous adj3 hemodiafiltration).tw. 12.(intermittent hemodialysis or IHD).tw. 13.(continuous adj3 hemodialysis).tw. 14.continuous ultrafiltration.tw. 15.(CVVH or CVVHDF or CVVHD or SCUF or CRRT).tw. 16.renal replacement therap$.tw. 17.(sustained low efficiency dialysis or SLED).tw. 18.(extended daily dialysis or EDD).tw. 19.hemoperfusion.tw. 20.or/8-19 21.and/7,20
EMBASE	1. acute kidney failure/ 2. (acute kidney failure or acute renal failure).tw. 3. (acute kidney injur$ or acute renal injur$).tw. 4. (acute kidney insufficie$ or acute renal insufficie$).tw. 5. acute tubular necrosis.tw. 6. (ARI or AKI or ARF or AKF or ATN).tw. 7. or/1-6 8. continuous renal replacement therapy/ or exp renal replacement therapy/ 9. (continuous adj3 hemofiltration).tw. 10.(continuous adj3 hemodiafiltration).tw. 11.(continuous adj3 h?emodialysis).tw. 12.continuous ultrafiltration.tw. 13.(CVVH or CVVHDF or CVVHD or SCUF or CRRT).tw. 14.(intermittent h?emodialysis or IHD).tw. 15.renal replacement therap$.tw. 16.(sustained low efficiency dialysis or SLED).tw. 17.(extended daily dialysis or EDD).tw. 18.hemoperfusion.tw. 19.or/8-18
LILACS	1. acute kidney failure/ 2. acute kidney failure or acute renal failure) tw

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(Continued)

3. acute tubular necrosis.tw.
4. or/1-3
5. continuous renal replacement therapy/
6. (continuous venovenous haemofiltration or continuous venovenous haemofiltration) tw.
7. (continuous venovenous haemodiafiltration or continuous venovenous haemodiafiltration) tw.
8. (continuous venovenous haemodialysis or continuous venovenous haemodialysis) tw.
9. or/5-8

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimisation (minimisation may be implemented without a random element, and this is considered to be equivalent to being random)
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention
	Unclear: Insufficient information about the sequence generation process to permit judgement
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes)
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure
	Unclear: Randomisation stated but no information on method used is available
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors.	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken

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(Continued)

	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data.	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. sub scales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study
	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free In order to show some aspects of the heterogeneity result, in this table we show other sources of bias
	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias

Appendix 3. Meta-regression

Stata 14.1 outputs exploring the effect of several explanatory variables on primary and secondary outcomes with six or more included studies:

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death at day 30, recovery of kidney function, length of hospital and ICU stay.

The covariates included in the models were: type of participant (**typepatient**); Fluid overload after randomisation in three categories(**catpat**); difference in the fluid overload after randomisation in the early group minus the standard group (**Dif**).

The explanatory variables were defined as follows:

1. **type of participants:** participant with AKI related to non-surgical cause versus participant with AKI related to surgical causes
2. **catpat**: categories considering the amount of fluid overload (FO) after randomisation between both groups, according to the following: mild:
3. FO<3 Lts (**icatpat0**); moderate: fluid overload between 3Lts to < 6 Lts (**icatpat1**); severe: fluid overload ≥ 6 Lts (**icatpat2**)
4. **Dif:** absolute difference in fluid overload after randomisation between the standard group minus fluid overload after randomisation in the intervention group
5. **Modal:** participant who receive CRRT modality and participant who receive both modalities (continuous and Intermittent)
6. **Hypot**: difference of percentage in number of patients with hypotension between early group minus standard group

We analysed several models for each outcomes. We present the model with the three covariates of each outcomes, including the full output of the STATA 14.1 statistics.

In each model the covariates were typed in bold (see definitions above). The other code in tables were:

1. **Logrr**: Relative risk of dichotomy outcomes
2. **ES**: mean difference of continuous outcomes
3. **Coef.**: value of the relative risk or the mean difference in their units
4. **P>t**: probability that the logrr difference adjusted by other covariates could be related to chance if P is higher than 0.05
5. **Std. Err**: standard error of the coefficient
6. **t**: test
7. **P>t**: probability that the logrr difference adjusted by other covariates could be related to chance if P is higher than 0.05(not significant)
8. **95% Conf. Interval**: 95% confidence interval of the logrr or ES values.

It is important to state the limitations of this meta-regression because of the limited studies (9) for the number of covariates in the model.

Death at day 30

. xi: metareg logrr **i.catpat typepatient dif,** wsse(selogrr) bsest(reml)

i.catpat _Icatpat_1-2 (naturally coded; _Icatpat_1 omitted)

note: _Icatpat_2 dropped because of collinearity

numerical derivatives are approximate

nearby values are missing

Meta-regression Number of obs = 6

REML estimate of between-study variance tau2 = 0

% residual variation due to heterogeneity I-squared_res = 0.00%

Proportion of between-study variance explained Adj R-squared = .%

Joint test for all covariates Model F(2,3) = 1.47

With Knapp-Hartung modification Prob > F = 0.3598

See. Appendix 4.1

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Death at day 30

. xi: metareg logrr **hipot typepatient dif,** wsse(selogrr) bsest(reml)

Meta-regression Number of obs = 9

REML estimate of between-study variance tau2 = 0

% residual variation due to heterogeneity I-squared_res = 31.02%

Proportion of between-study variance explained Adj R-squared = .%

Joint test for all covariates Model F(3,5) = 0.93

With Knapp-Hartung modification Prob > F = 0.4902

See. Appendix 4.2

Death at day 30

. metareg logrr **hipot typepatient dif modal**, wsse(selogrr) bsest(reml)

Meta-regression Number of obs = 9

REML estimate of between-study variance tau2 = 0

% residual variation due to heterogeneity I-squared_res = 44.13%

Proportion of between-study variance explained Adj R-squared = .%

Joint test for all covariates Model F(4,4) = 0.58

With Knapp-Hartung modification Prob > F = 0.6954

See. Appendix 4.3

Recovery of Kidney function in all patients

. xi: metareg logrr**i.catpat typepatient dif,** wsse(selogrr) bsest(reml)

i.catpat _Icatpat 1-2 (naturally coded; _Icatpat_1 omitted)

Meta-regression Number of obs = 6

REML estimate of between-study variance tau2 = .007724

% residual variation due to heterogeneity I-squared_res = 11.26%

Proportion of between-study variance explained Adj R-squared = 44.71%

Joint test for all covariates Model F (3,2) = 1.42

With Knapp-Hartung modification Prob > F = 0.4389

See. Appendix 5.1

Renal recovery function in all patients

. metareg logrr **hipot typepatient dif**, wsse(selogrr) bsest(reml)

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Meta-regression Number of obs = 9

REML estimate of between-study variance tau2 = .01708

% residual variation due to heterogeneity I-squared_res = 53.90%

Proportion of between-study variance explained Adj R-squared = -214.78%

Joint test for all covariates Model F(3,5) = 0.32

With Knapp-Hartung modification Prob > F = 0.8136

See. Appendix 5.2

Renal recovery function in all patients

metareg logrr **hipot typepatient dif modal**, wsse(selogrr) bsest(reml)

Meta-regression Number of obs = 9

REML estimate of between-study variance tau2 = .02433

% residual variation due to heterogeneity I-squared_res = 59.28%

Proportion of between-study variance explained Adj R-squared = -348.52%

Joint test for all covariates Model F(4,4) = 0.30

With Knapp-Hartung modification Prob > F = 0.8624.

See. Appendix 5.3

Length at hospital stay

metareg **typepatient modal**, wsse(_seES) bsest(reml)

Meta-regression Number of obs = 7

REML estimate of between-study variance tau2 = .1255

% residual variation due to heterogeneity I-squared_res = 76.81%

Proportion of between-study variance explained Adj R-squared = 47.28%

With Knapp-Hartung modification

See Appendix 6

Appendix 4. Death at day 30

Appendix 5.1

logrr [a]	Coef.	Std. Err.	t	P>|t|	[95% CI]	
typepatient	-.3186244	.1861809	-1.71	0.186	-.911135	.2738862
dif	1.66e-06	.0001456	0.01	0.992	-.0004616	.0004649

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(Continued)

_cons	.033581	.0862504	0.39	0.723	-.2409064	.3080684

[a] Relative Risk

Interpretation of Death at day 30. None of the covariates had a statistically significant influence on the size of the effect of the interventions on death at day 30.

Appendix 5.2

logrr [a]	Coef.	Std. Err.	t	P>|t|	[95% CI]	
hypot	.0795709	.1422428	0.56	0.600	-.2860758	.4452176
typepatient	-.3100715	.2049243	-1.51	0.191	-.8368462	.2167031
dif	-.0001102	.0005975	-0.18	0.861	-.0016461	.0014257
_cons	-.0309248	.1053141	-0.29	0.781	-.30164331	.2397937

[a] Relative Risk

Interpretation of Death at day 30. None of the covariates had a statistically significant influence on the size of the effect of the interventions on death at day 30

Appendix 5.3

logrr [a]	Coef.	Std. Err.	t	P>|t|	[95% CI]	
hypot	.069663	.1635693	0.43	0.692	-.3844781	.5238041
typepatient	-.3454696	.2777644	-1.24	0.282	-1.116667	.4257279
dif	-0.000345	.0006119	-0.06	0.958	-.0017335	.0016644
modal	.0467809	.2107168	0.22	0.835	-.5382627	.6318246
_cons	-.0349755	.1184264	-0.30	0.782	-.36378	.293829

[a] Relative Risk

Interpretation of Death at day 30. None of the covariates had a statistically significant influence on the size of the effect of the interventions on death at day 30

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Appendix 5. Recovery of kidney function

Appendix 6.1

logrr [a]	Coef.	Std. Err.	t	P>|t|	[95% CI]	
_Icatpat_2	-.3157028	.1875572	-1.68	0.234	-1.1222696	.4912907
typepatient	-.0293159	.0838276	-0.35	0.760	-.3899969	.3313651
dif	.0001913	.0002193	0.87	0.475	-.0007524	.001135
_cons	.2599936	.1970522	1.32	0.318	-.5878537	1.107841

[a] Relative Risk

Interpretation of recovery of kidney function in all patients

None of the covariates had a statistically significant influence on the size of the interventions effect on the recovery of kidney function in all patients

Appendix 6.2

logrr [a]	Coef.	Std. Err.	t	P>|t|	[95% CI]	
hypot	.0354318	.2072378	0.17	0.871	-.4972899	.5681535
typepatient	.1498447	.222515	.067	0.531	-.4221483	.7218376
dif	-.0005543	.0011819	-0.47	0.659	-.0035926	.0024839
_cons	.0209444	.1732834	0.12	0.909	-.4244948	.466638

[a] Relative Risk

Interpretation of recovery of Kidney function in all patients

None of the covariates had a statistically significant influence on the size of the interventions effect on the recovery of kidney function in all patients

Appendix 6.3

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(Continued)

logrr [a]	Coef.	Std. Err.	t	P>|t|	[95% CI]	
hypot	.0176247	.2349727	0.08	0.944	-.6347642	.6700136
typepatient	-.0646383	.40121183	-0.16	0.880	-1.178599	1.049322
dif	-.0003625	.0014235	-0.25	0.812	-.0043147	.0035898
modal	.2536712	.3719964	0.68	0.533	-.7791565	1.286499
_cons	-.0024396	.2045583	-0.01	0.991	-.5703845	.5655053

[a] Relative Risk

Interpretation of recovery of kidney function in all patients

None of the covariates had a statistically significant influence on the size of the interventions effect on the recovery of kidney function in all patients

Appendix 6. Length of hospital stay

logrr [a]	Coef.	Std. Err.	t	P>|t|	[95% CI]	
modal	.6735466	.3149659	2.14	0.085	-.1360991	1.483192
_cons	5.55e-17	.2171838	0.00	1.000	-.5582888	.5582888

[a] Relative Risk

Interpretation of length of hospital stay

None of the covariates had a statistically significant influence on the size of the effect of the interventions on the length of hospital stay

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Appendix 7. Database of death at day 30

Trialname	cases1	tot1	case0	tot0	hypot	typepa-tient	modal	catpat	dif
ELAIN 2016	34	112	48	119	0.96	1	1	1	500
IDEAL-ICU 2014	111	246	102	242	11.35	0	0	2	120
FST 2018	36	58	35	60	14.5	0	1	2	351
STARRT-AKI Pilot 2013	13	48	16	52	-1	0	0	2	61
STARRT-AKI 2019	538	1465	523	1462	5.67	0	0	2	601
AKIKI 2015	129	311	134	308	0	0	0	-	0
EARLYRRT 2018	10	20	9	20	0	0	0	-	2220
Sugahara 2004	2	14	12	14	0	1	1	-	0
Bouman 2002	20	70	9	36	0	1	1	-	0

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Appendix 8. Database of recovery of kidney function

Trialname	cases1	tot1	case0	tot0	hypot	typepa-tient	modal	dif	catpat
Bouman 2002	38	70	22	36	0.96	1	1	500	1
ELAIN 2016	60	112	46	119	11.35	1	1	120	2
IDEAL-ICU 2014	106	246	111	242	14.5	0	0	351	2
FST 2018	21	58	19	60	-1	0	1	61	2
STARRT-AKI Pilot 2013	30	48	31	52	5.67	0	0	601	2
STARRT-AKI 2019	729	1465	766	1462	0	0	0	0	2
AKIKI 2015	154	311	147	308	0	0	0	2220	-
EARLYRRT 2018	9	20	5	20	0	0	1	0	2
Sugahara 2004	10	14	2	14	0	1	1	0	-

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Appendix 9. Database of hospital length of stay

Trialname	mean1	SD1	tot1	mean2	SD2	tot2	typepatient	modal
Bouman 2002	27	21	70	35.5	38.5	36	1	1
ELAIN 2016	44.2	41.9	112	64.6	70.6	119	1	1
IDEAL-ICU 2014	31	46.9	311	28.4	35.5	308	0	0
FST 2018	29.7	35.5	58	32.6	34.9	60	0	1
STARRT-AKI Pilot 2013	32.1	41.4	48	28.9	28.1	52	0	0
STARRT-AKI 2019	31.33	25.24	1465	33.329	27.47	1462	0	0
AKIKI 2015	31	46.9	311	28.4	35.5	308	0	0

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Appendix 10. Database for meta-regression

We conducted the meta-regressions of each of the outcomes according to the following databases. The codes used to identify each column of the databases were:

1. **trial name** study ID
2. **cases1**: number of events in the intervention group
3. **cases0** : number of events in the control group
4. **tot1**: number of participants in the intervention group
5. **tot0**: number of participants in the control group
6. **mean1**: mean value in the intervention group
7. **SD1**: standard deviation in the intervention group
8. **mean2**: mean value in the control group
9. **SD 2:** standard deviation in the control group
10. **dif**: absolute difference in fluid overload between the control minus the intervention group.
11. **catpat**: categories according the amount of fluid overload (FO) after randomisation between both group. **mild:** FO < 3 L (**catpat0**);
12. **moderate**: FO 3 to < 6 L (**catpat1**) and **severe**: FO ≥ 6 L (**catpat2**)
13. **typepatient**: participants with surgical-AKI=1; participants with non related surgical AKI=0
14. **modal.**: KRT modality predominant continuous KRT= 1 and combined continuous + intermittent KRT.:=0
15. **hipot.**: percentage of patients with hypotension in early group minus percentage of patients with hypotension in standard group (%).

See Appendix 7; Appendix 8; Appendix 9

WHAT'S NEW

Date	Event	Description
4 August 2022	New citation required and conclusions have changed	New studies added
4 August 2022	New search has been performed	New search, new studies added

HISTORY

Protocol first published: Issue 6, 2013
Review first published: Issue 12, 2018

Date	Event	Description
26 September 2017	New search has been performed	Search strategies for MEDLINE, EMBASE & CENTRAL updated to reflect change in title

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: AF, DB, AC
2. Study selection: AF, DB
3. Extract data from studies: AF, DB
4. Enter data into RevMan: AF

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5. Carry out the analysis: AF, AC
6. Interpret the analysis: AF, DB, AC
7. Draft the final review: AF, DB, AC
8. Disagreement resolution: AC
9. Update the review: AF

DECLARATIONS OF INTEREST

- Alicia I Fayad: no relevant interests were disclosed
- Daniel G Buamscha: no relevant interests were disclosed
- Agustín Ciapponi: no relevant interests were disclosed

SOURCES OF SUPPORT

Internal sources

- No internal sources of support, Other

External sources

- Instituto de Efectividad Clínica y Sanitaria (Institute for Clinical Effectiveness and Health Policy) (IECS-CONICET), Argentina

  The Institute for Clinical Effectiveness and Health Policy (IECS-CONICET) is an independent, non-for-profit organization devoted to research, education and technical support (www.iecs.org.ar). Over the last few years, IECS has been a leading institution in Latin America (LA) in regards to developing HTA reports and economic evaluations (EE) to study the impact and financial implications of the adoption of technologies on health care systems.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We modified the title of our review "Timing of ***Kidney replacement therapy*** initiation for acute kidney injury"

Inclusion criteria: we included all patients with AKI in ICU being treated with ***kidney replacement therapy*** regardless of age and gender.

Measures of treatment effect: These results were interpreted with focus on effect size of the central estimation (magnitude or importance), including clinical relevance (CKT 2017; EPOC 2013); and decrease the reliance to report on statistical significance (P value) that only provides an arbitrary binary approach (Ciapponi 2021).

The confidence intervals are considered for the GRADE certainty evidence related to the domain imprecision (CKT 2017; EPOC 2013; Schunemann 2021a).

INDEX TERMS

Medical Subject Headings (MeSH)

*Acute Kidney Injury [etiology] [therapy]; Critical Illness; Kidney; Length of Stay; *Renal Replacement Therapy [adverse effects]

MeSH check words

Humans

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