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Intensity of continuous renal replacement therapy for acute kidney injury (Review)

Fayad AI, Buamscha DG, Ciapponi A

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[Intervention Review]

Intensity of continuous renal replacement therapy for acute kidney injury

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ABSTRACT

Background

Acute kidney injury (AKI) is a common condition among patients in intensive care units (ICU), and is associated with substantial morbidity and mortality. Continuous renal replacement therapy (CRRT) is a blood purification technique used to treat the most severe forms of AKI but its effectiveness remains unclear.

Objectives

To assess the effects of different intensities (intensive and less intensive) of CRRT on mortality and recovery of kidney function in critically ill AKI patients.

Search methods

We searched Cochrane Kidney and Transplant's Specialised Register to 9 February 2016 through contact with the Information Specialist using search terms relevant to this review. Studies contained in the Specialised Register are identified through search strategies specifically designed for CENTRAL, MEDLINE, and EMBASE; handsearching conference proceedings; and searching the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov. We also searched LILACS to 9 February 2016.

Selection criteria

We included all randomised controlled trials (RCTs). We included all patients with AKI in ICU regardless of age, comparing intensive (usually a prescribed dose ≥35 mL/kg/h) versus less intensive CRRT (usually a prescribed dose < 35 mL/kg/h). 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 differences (MD) for continuous outcomes, with 95% confidence intervals (CI).

Main results

We included six studies enrolling 3185 participants. Studies were assessed as being at low or unclear risk of bias. There was no significant difference between intensive versus less intensive CRRT on mortality risk at day 30 (5 studies, 2402 participants: RR 0.88, 95% CI 0.71 to 1.08; I^2 = 75%; *low quality of evidence*) or after 30 days post randomisation (5 studies, 2759 participants: RR 0.92, 95% CI 0.80 to 1.06; I^2 = 65%; *low quality of evidence*). There were no significant differences between intensive versus less intensive CRRT in the numbers of patients who were free of RRT after CRRT discontinuation (5 studies, 2402 participants: RR 1.12, 95% CI 0.91 to 1.37; I^2 = 71%; *low quality of evidence*) or among survivors at day 30 (5 studies, 1415 participants: RR 1.03, 95% CI 0.96 to 1.11; I^2 = 69%; *low quality of evidence*) and day 90 (3 studies, 988 participants: RR 0.98, IC 95% 0.94 to 1.01, I^2 = 0%; moderate*quality of evidence*). There were no significant differences between intensive and less intensive CRRT on the number of days in hospital (2 studies, 1665 participants): MD -0.23 days, 95% CI -3.35 to 2.89; I^2 = 8%; *low quality of evidence*) and the number of days in ICU (2 studies, 1665 participants: MD -0.58 days, 95% CI -3.73 to 2.56, I^2 = 19%; *low quality of evidence*). Intensive CRRT increased the risk of hypophosphataemia (1 study, 1441 participants: RR 1.21, 95% CI 1.11 to 1.31; *high quality evidence*) compared to less intensive CRRT. There was no significant differences between intensive and less intensive CRRT on numbers of patients who experienced adverse events (3 studies, 1753 participants: RR 1.08, 95% CI 0.73 to 1.61; I^2 = 16%; *moderate quality of evidence*). In the subgroups analysis by severity of illness and by aetiology of AKI, intensive CRRT would seem to reduce the risk mortality (2 studies, 531 participants: RR 0.73, 95% CI 0.61 to 0.88; I^2 = 0%; *high quality of evidence*) only in the subgroup of patients with post-surgical AKI.

Authors' conclusions

Based on the current low quality of evidence identified, more intensive CRRT did not demonstrate beneficial effects on mortality or recovery of kidney function in critically ill patients with AKI. There was an increased risk of hypophosphataemia with more intense CRRT. Intensive CRRT reduced the risk of mortality in patients with post-surgical AKI.

PLAIN LANGUAGE SUMMARY

Intensity of continuous renal replacement therapy for acute kidney injury

What is the issue?

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

Continuous renal replacement therapy (CRRT) is a blood purification technique that enables removal of excess water and toxins. CRRT involves blood being diverted from the patient via a catheter (a hollow, flexible tube placed into a vein) through a filtering system which continuously and steadily removes excess water and toxins; purified blood is then returned to the patient via the catheter. Higher intensity CRRT improves the removal of toxins and excess water. The aim of this review was to investigate the effect of different intensities of CRRT (intensive or less intensive) 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 February 2016 and identified six studies enrolling 3185 patients with AKI that were evaluated in this review.

What did we find?

Six randomised studies enrolling 3185 participants were included in our review. Compared to less intensive CRRT, intensive CRRT did not reduce the risk of death, improve the recovery of kidney function, or reduce the risk of adverse events (such as bleeding) in patients with AKI. Intensive CRRT was associated with an increased risk of low blood phosphate levels.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Intensive versus less intensive CRRT for AKI

Patient or population: patients with AKI
Settings: ICU
Intervention: Intensive versus less intensive CRRT

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Less intensive CRRT	Intensive CRRT				
Mortality at day 30 Follow-up: 30 days	**Study population**		**RR 0.88** (0.81 to 1.1)	2402 (5)	⊕⊕◯◯ **low**[1,2]	
	430 per 1000	**420 per 1000** (412 to 523)				
	Moderate					
Mortality after 30 days post-randomisation Follow-up: 60 days	**Study population**		**RR 0.92** (0.80 to 1.06)	2759 (5)	⊕⊕◯◯ **low**[1,2]	
	514 per 1000	**483 per 1000** (416 to 565)				
	Moderate					
	593 per 1000	**557 per 1000** (480 to 652)				
Patients free of RRT after discontinuing CRRT Follow-up: 30 days	**Study population**		**RR 1.12** (0.91 to 1.37)	2402 (5)	⊕⊕◯◯ **low**[1,2]	

	483 per 1000	**541 per 1000** (439 to 661)			
	Moderate				
	390 per 1000	**437 per 1000** (355 to 534)			
Patients free of RRT after discontinuing CRRT Follow-up: 90 days	**Study population**		**RR 0.98** (0.94 to 1.01)	988 (3)	⊕⊕⊕○ **moderate**[3]
	923 per 1000	**904 per 1000** (867 to 932)			
	Moderate				
	800 per 1000	**784 per 1000** (752 to 808)			
Adverse events: hypophosphataemia	**Study population**		**RR 1.21** (1.11 to 1.31)	1441 (1)	⊕⊕⊕⊕ **high**
	540 per 1000	**654 per 1000** (600 to 708)			
	Moderate				
	540 per 1000	**653 per 1000** (599 to 707)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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/s; **RR:** Risk ratio; **RRT**: renal replacement therapy

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] inconsistency: due to substantial heterogeneity (I^2 values ranged from 73% to 78%)

[2] imprecision: due to wide CI which crossed the threshold for clinically meaningful effects

[3] Indirectness: critically ill patients with AKI in CRRT have high short-term mortality risk; mortality is a competing end point for kidney recovery at day 90

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 (ICU) range from 5% to 20% (Hoste 2006; 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 mortality (Bagshaw 2007). AKI-related mortality substantially increases among people with multi-organ failure, sepsis or who are receiving renal replacement therapy (RRT) (Metnitz 2002; Sutherland 2010). More than 70% of people with AKI need renal support therapies. Despite advances in clinical care, people with AKI are at high risk of mortality and morbidity, and require significant healthcare resources (Sutherland 2010; Uchino 2005).

Description of the intervention

Continuous renal replacement therapy (CRRT) is an extracorporeal blood purification therapy, intended to support impaired kidney function. CRRT slowly removes fluid over prolonged periods (Foland 2004; Gibney 2008; Goldstein 2001; Mehta 1999), removes higher molecular weight solutes efficiently (Brunnet 1999; Clark 1999; Liao 2003; Ronco 2002; Sieberth 1995), and confers beneficial haemodynamic stability effects. CRRT modalities are defined by their main solute clearance mechanism. These are convection (continuous venovenous haemofiltration (CVVH)), diffusion (continuous venovenous haemodialysis (CVVHD)), or a combination of both convection and diffusion (continuous venovenous haemodiafiltration, CVVHDF) (Palevsky 2002). Several interventions have been used over the past three decades with the aim of improving poor prognoses of people with AKI. A significant factor that may impact on CRRT outcomes is intensity of treatment (timing of CRRT for AKI is being investigated in another Cochrane review, Fayad 2013a).

CRRT intensity is generally related to the quantity of solute removal required to improve outcomes in people with AKI. CRRT intensity can be analysed based either on solute removal from the blood, or appearance of solutes in effluent fluid. Some published studies have used effluent flow rates, expressed as total effluent volume/weight and unit of time (mL/kg/h), as a dose surrogate (RENAL Study 2006; Ronco 2000a), while accounting for effects of pre-dilution and modality differences (Claure-Del Granado 2011). Elsewhere, authors have considered that dialysis doses delivered as total effluent volume/clearance of solutes such as urea, creatinine is a better method to measure dose (Lyndon 2012). Equivalent renal urea clearance also provides a good estimate of delivered dialysis dose in CRRT (Claure-Del Granado 2012) which can be converted to effluent rate and expressed as mL/kg/h (Marshall 2006).

Few studies have assessed other dimensions of dose such as electrolyte and acid-base homeostasis (Bellomo 2013; Bihorac 2005; Morimatsu 2003; Uchino 2001) and fluid balance/fluid overload (Bouchard 2009; Davenport 2010; Sutherland 2010) using effluent volume as the dose measure.

How the intervention might work

A hypothesis that high intensity of RRT may improve survival has emerged from animal and human studies. These findings include indirect evidence from patients with ESKD (Lowrie 1981; Parker 1994).

Intensity based on a urea kinetics model was evaluated in animal studies by Grootendorst 1992, and in severe ill patients (sepsis, sepsis-shock) who received high dose (60 to 80 mL/kg/h) reported improvement in haemodynamic state with possible benefits in clinical outcomes (Honore 2000). A retrospective study found that dose correlated with survival in patients with intermediate scores of illness (Paganini 1996). Although prospective dose studies demonstrated association of improved survival or kidney recovery with high dose dialysis (Phu 2002; Ronco 2000a; Saudan 2006), these advantages were not universally observed (ATN Study 2005; Negash 2011; RENAL Study 2006; Vesconi 2009; Van Wert 2010).

Few studies have researched other components of dose that play important roles in clinical results. These include fluid balance and fluid overload associated with increased mortality risk (Bouchard 2009; Goldstein 2001), adequate homeostasis of electrolytes (sodium, potassium and hydrogen ions) related to cardiovascular stability, and the maintenance of kidney blood flow (Uchino 2001).

Why it is important to do this review

Studies assessing CRRT intensity (intensive versus less intensive) have either not reported investigation of all variables inherent in therapy for people with AKI or report inconsistent results. We investigated the relationship between different intensities of CRRT and clinical outcomes for people with AKI. Review evidence could have direct relevance to decisions about optimal intensity of CRRT to improve survival in critically ill patients with AKI.

OBJECTIVES

To assess the effects of different intensities (intensive and less intensive) of CRRT on mortality and recovery of kidney function in critically ill AKI patients.

METHODS

Criteria for considering studies for this review

Types of studies

All RCTs and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) looking at CRRT modalities for people with AKI in ICU settings were eligible for inclusion. For outcomes such us safety and costs, non-RCTs and cohort studies were also to be included if sufficiently high quality, sampling was clearly described, patients characterised, proportions of patients experiencing any adverse events or who dropped out because of adverse events was 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 ICU being treated with CRRT regardless of age or 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 intensive (usually a prescribed dose $\geq$ 35 mL/kg/h) versus less intensive CRRT (usually a prescribed dose < 35 mL/kg/h). These categories of intensities were defined as published in the original publications. We included all CRRT modalities (CVVH, CVVHD and CVVHDF).

Types of outcome measures

Primary outcomes

Death

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

Recovery of kidney function

- Numbers of patients free of RRT after discontinuing CRRT
- Numbers of patients free of RRT after discontinuing CRRT at days 30, 60, and 90.

Secondary outcomes

Metabolic balance

- Numbers of patients who normalised serum electrolytes (potassium, sodium) concentration during CRRT
- Numbers of patients who normalised serum bicarbonate and base-excess concentration during CRRT
- Numbers of patients who normalised serum urea and creatinine concentration during CRRT.

Fluid balance

- Numbers of patients who achieved adequate fluid balance during CRRT.

Adverse events

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

We looked for differences in overall dropout 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 costs of CRRT modalities including:

- Type and number of dialyser filters
- Use/no use of anticoagulation
- Types of anticoagulation and anticoagulants
- Use of replacement fluid
- Numbers of days on CRRT.

All costs were to be reported in international monetary units.

- Cost per day of CRRT (expressed in international monetary units)
- Length of hospital stay with CRRT
- Length of ICU stay with CRRT.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Kidney and Transplant Specialised Register to 9 February 2016 through contact with the Information Specialist using search terms relevant to this review. The Specialised Register contains studies identified from the following sources.

1. Quarterly 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 of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney 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 currents awareness alert, available in the Specialised Register section of information about Cochrane Kidney and Transplant.

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

Searching other resources

1. LILACS (Latin American and Caribbean Health Sciences) (from March 1980 to February 2016)
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 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 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 discrepancy by discussion.

Assessment of risk of bias in included studies

The following items were independently assessed using the risk of bias assessment tool (Higgins 2011) (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 a 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 (mortality, 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.

Dealing with missing data

Any further information required from the original author was requested by written correspondence (e.g. emailing 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 2011).

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 2011).

Data synthesis

Data were pooled using the random-effects model but the fixed-effect model was also used to ensure 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, participant and study quality). Heterogeneity among participants could relate to age, gender, fluid overload (< 10% and > 10% body weight relative to baseline), Intensive CRRT for AKI in homogenous subpopulations such as cardiac surgery or sepsis patients, effects of intensive continuous therapy on severity of illness - high, intermediate and low. 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).

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 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, language of publication, source of funding (industry versus other), and country.

'Summary of findings' tables

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 (Schünemann 2011a). The 'Summary of findings' tables also 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). 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 of specific interest. The quality of a body of evidence involves consideration of within-study risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias (Schünemann 2011b). Two summary of findings tables were created. Summary of findings for the main comparison summarizes the main findings for the comparison "Intensive versus less intensive RRT for acute kidney injury". We presented the following outcomes.

- Mortality until day 30 post-randomisation
- Mortality after 30 days post-randomisation
- Kidney function recovery: number of patients free of RRT after discontinuing CRRT
- Kidney function recovery: number of patients free of RRT after discontinuing CRRT until day 90, among survivals
- Adverse events: number of patients with hypophosphataemia

Summary of findings 2 summarizes the main mortality findings for the subgroups of patients with AKI with and without sepsis, and related or not to surgery.

RESULTS

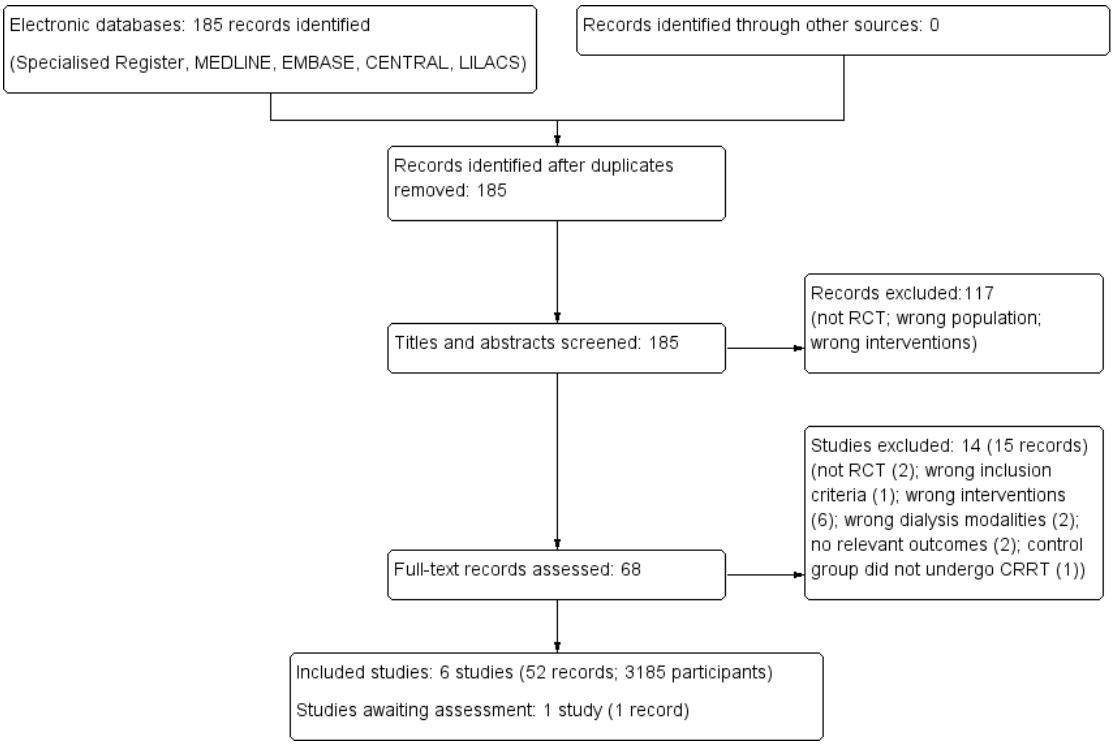
Description of studies

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

Results of the search

We identified 185 records from electronic databases (MEDLINE, EMBASE, CENTRAL, Cochrane Kidney and Transplant's Specialised Register, LILACS) to 9 February 2016. We screened these titles and abstracts excluded 117 records. We assessed the full text of 68 potentially eligible records (21 studies). Six studies (52 records) were included in our review (ATN Study 2005; Bouman 2002; RENAL Study 2006; Ronco 2000a; Saudan 2006; Tolwani 2008). One study has recently been completed but no results have been published (NCT01560650). Fourteen studies (15 records) were excluded (Figure 1). There was no disagreement among authors regarding inclusion of studies.

Figure 1. Study flow diagram



Included studies

Six included studies (ATN Study 2005; Bouman 2002; RENAL Study 2006; Ronco 2000a; Saudan 2006; Tolwani 2008) enrolled a total of 3185 participants.

Study participants were all admitted to ICU. The mean age ranged from 51 and 68 years, and the proportion of male ranged from 55% to 71%. Sepsis was the primary cause of AKI in four studies (ATN Study 2005; RENAL Study 2006; Saudan 2006; Tolwani 2008) and surgery or cardio-surgery the main cause in the other two (Bouman 2002; Ronco 2000a)

All studies were reported between 2000 and 2008. Three were single-centre studies (Ronco 2000a; Saudan 2006; Tolwani 2008) and three were multicentre (ATN Study 2005; Bouman 2002; RENAL Study 2006).

Four studies used one CRRT modality exclusively; RENAL Study 2006 and Tolwani 2008 used CVVHDF, and Bouman 2002 and Ronco 2000a used CVVH. Saudan 2006 used CVVH and CVVHDF and ATN Study 2005 used intermittent haemodialysis (IHD) and CVVHDF or sustained low-efficiency haemodialysis (SLED), depending on the haemodynamic stability of the participant. Replacement fluid was administered either pre filter (ATN Study 2005; Saudan 2006; Tolwani 2008) or post filter (Bouman 2002; Ronco 2000a; RENAL Study 2006) when either CVVH or CVVHDF were used.

Five studies assessed the effects of two intensities of continuous therapy (ATN Study 2005; Bouman 2002; RENAL Study 2006; Saudan 2006; Tolwani 2008), whereas one assessed the effects of three CRRT intensities (standard, intermediate and high) (Ronco 2000a). For the purpose of the analysis, we combined the intermediate with high-dose arm of this study to create one high intensity arm. In Bouman 2002, two arms received the same less intensive CRRT dose but differed only in the timing of CRRT initiation. We combined these two treatment arms to create one less intensive arm. ATN Study 2005 randomly assigned critically ill patients with AKI to high-intensity or low-intensity RRT. Within treatment groups, patients were allocated to intermittent (IHD) or prolonged (SLED) and continuous RRT according to cardiovascular SOFA score. Continuous RRT was provided to 69.7% of patients as their initial therapy. However, unstable patients assigned to CRRT had a variable number of switches in treatment modality: none (36.1%) or 1 (24%) and $\geq$ 2 modalities (10%) (Palevsky 2009). For the purpose of the analysis, we included all patients initially allocated to continuous CRRT independently of the switches in treatment modality (intention-to-treat analysis), who survived to day 60.

Five studies prescribed dose according to patients' weight at the time of admission (ATN Study 2005; RENAL Study 2006; Ronco 2000a; Saudan 2006; Tolwani 2008), and only one prescribed dose per unit of time (Bouman 2002).

Overall, the prescribed dose of CRRT in the less intensive arm of included studies ranged between 20 to 25 mL/kg/h and in intensive arm ranged between 35 to 48 mL/kg/h.

For full details see Characteristics of included studies.

Excluded studies

Fourteen studies were excluded. Cole 2002 and Vesconi 2009 compared continuous dialysis therapy versus no haemofiltration or other RRT (intermittent haemodialysis). Boussekey 2008, IVOIRE Study 2013, Sanchez 2010b and Zhang 2012 and two ongoing studies (NCT01191905; NCT01251081) compared different intensity-arms treatment. Ghani 2006 and Payen 2009 did not provide relevant outcomes for this review. Two studies were not RCTs (Brause 2003; Zha 2012). In HEROICS Study 2015, 36% of control-arm patients did not receive CRRT. Jiang 2005 had different inclusion criteria in relation to our review. Only six patients (16%) with severe pancreatitis have AKI and were treated with CRRT (Characteristics of excluded studies).

Risk of bias in included studies

Included studies were generally at low or unclear risk of bias for all domains (See Figure 2; Figure 3).

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

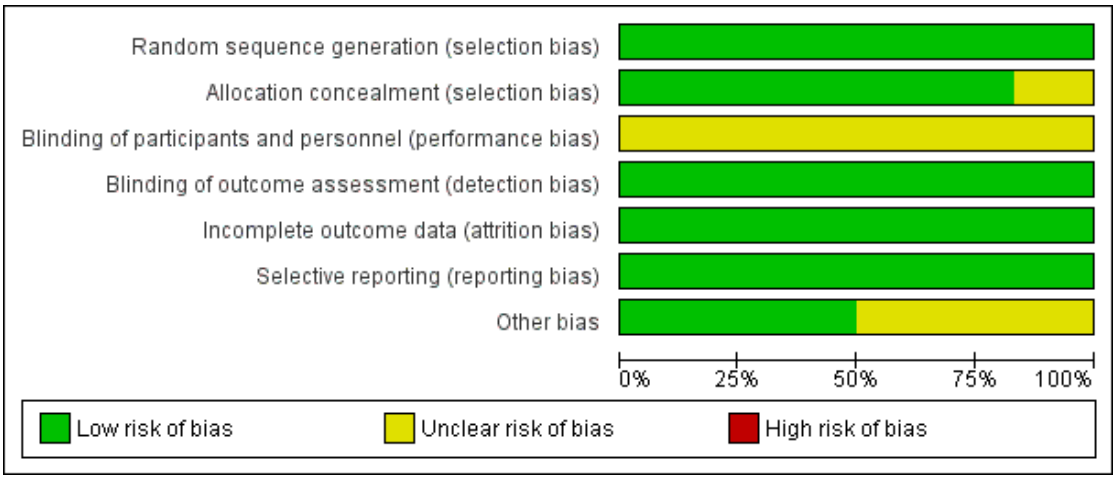
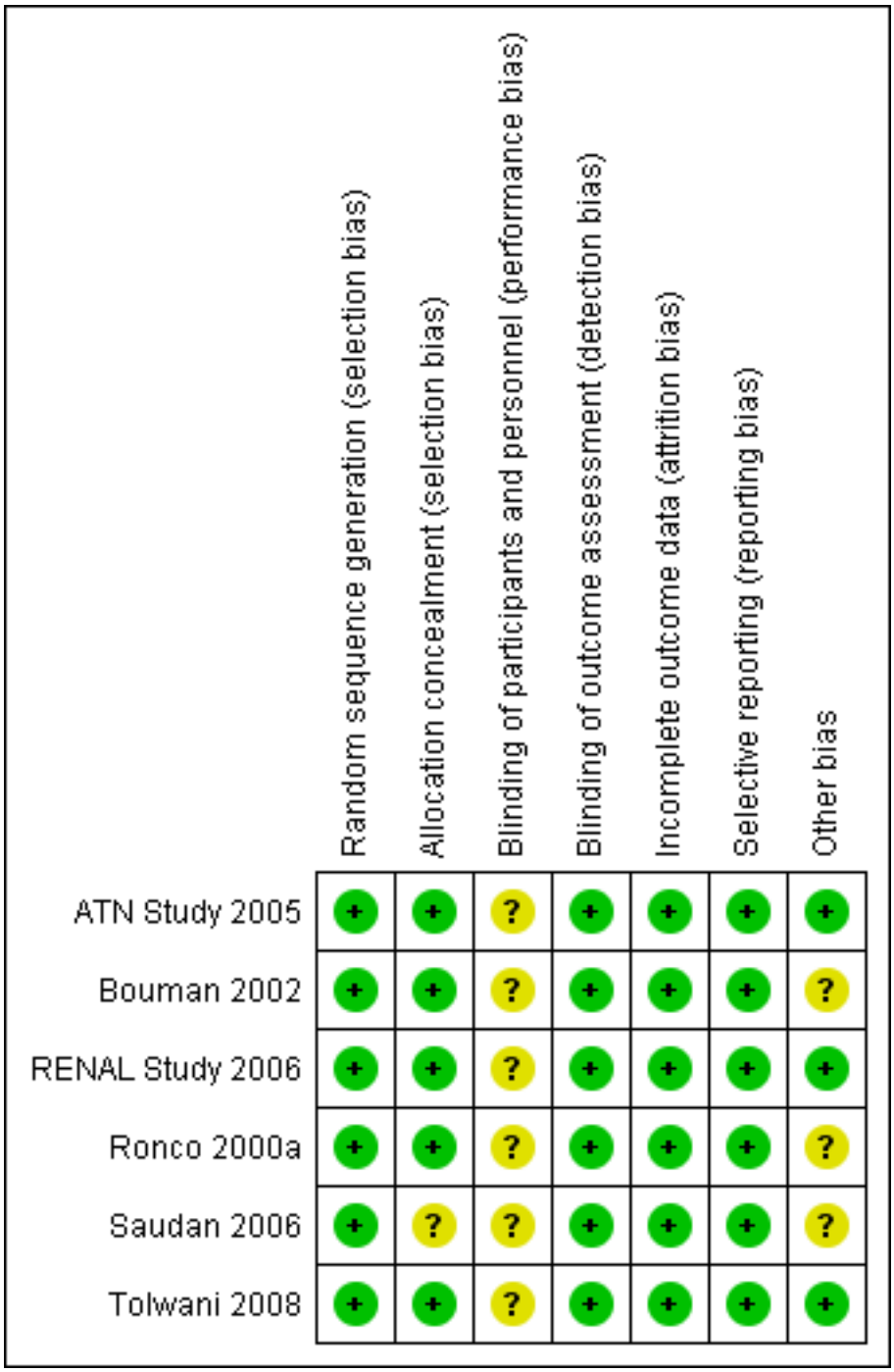


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study



Allocation

Bouman 2002 and Ronco 2000a did not provide detailed information about random sequence generation and allocation concealment processes. Authors were contacted and we were informed that the random sequence generation was appropriate (computer-generated) and sealed opaque envelopes were used for the allocation process. All studies were assessed as being at low risk of selection bias due to appropriate random sequence generation and five were allocation concealment processes. The allocation process was considered unclear in Saudan 2006 due to disease severity imbalance observed between the study arms.

Blinding

All included studies were assessed at low risk of detection bias (outcome measurement was unlikely to be influenced by lack of blinding), and unclear risk of performance bias (insufficient information to enable judgment).

Incomplete outcome data

The risk of attrition bias was low in all included studies. Intention-to-treat analysis was performed in all studies.

Selective reporting

Published records included all expected outcomes and were considered at low risk of bias.

Other potential sources of bias

Three studies provided complete information on grant support for authors and studies (ATN Study 2005; RENAL Study 2006; Tolwani 2008). This information was unclear in the remaining three studies.

Effects of interventions

See: **Summary of findings for the main comparison** Intensive versus less intensive continuous renal replacement therapy (CRRT) for acute kidney injury (AKI); **Summary of findings 2** Intensive versus less intensive continuous renal replacement therapy (CRRT) for acute kidney injury (AKI): subgroups

The effects of intensive CRRT versus less intensive CRRT for main results and the quality of the evidence are summarised in Summary of findings for the main comparison

Mortality

All six studies assessed the effect of different intensities of CRRT (intensive versus less intensive treatment) on mortality. These studies varied in mortality reporting timing: at 90 days (RENAL Study 2006; Saudan 2006), 60 days (ATN Study 2005), 28 days after randomisation or at ICU discharge (Bouman 2002; Tolwani 2008), and 15 days after cessation of CRRT (Ronco 2000a).

There was no significant difference between intensive versus less intensive CRRT on mortality risk at day 30 (Analysis 1.1.1 (5 studies, 2402 participants): RR 0.88, 95% CI 0.71 to 1.08; I^2 = 75%) or after 30 days post randomisation (Analysis 1.1.2 (5 studies, 2759 participants): RR 0.92, 95% CI 0.80 to 1.06; I^2 = 65%). There was substantial heterogeneity among studies**.** We downgraded the quality of evidence from high to low due to this inconsistency and imprecision (Summary of findings for the main comparison).

Subgroup analysis and investigation of heterogeneity

There was evidence of significant heterogeneity in the magnitude of the effect among the included studies that measured mortality at different times of randomisation (at day 30 and after 30 days). To assess heterogeneity among participants we planned to perform the following pre-specified subgroup analyses: by age, gender, fluid overload (≤ 10% and > 10% in body weight relative to baseline*),* according to aetiology of AKI and severity of illness. Only data for aetiology of AKI and severity of illness were available.

The effect of the severity of illness at baseline was assessed using two subgroups: patients with and without sepsis and patients with high and low SOFA cardiovascular scores (≥ 3 and < 3). The was no significant differences in mortality between intensive versus less intensive CRRT in patients with sepsis (Analysis 1.2.1 (5 studies, 966 participants): RR 0.94; 95% CI 0.69 to 1.27; I^2 = 72%) or without sepsis (Analysis 1.2.2 (4 studies, 1216 participants): RR 0.89, 95% CI 0.69 to 1.15; I^2 = 73%), or in patients with SOFA scores < 3 (Analysis 1.2.3; 1 study, 404 participants: RR 0.91, 95% CI 0.71 to 1.18) or SOFA score ≥ 3 (Analysis 1.2.4; 1 study, 1056 participants: RR 1.04, 95% CI 0.92 to 1.18).

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 less intensive CRRT, Intensive CRRT reduced the risk of death in patients with post-surgical AKI (Analysis 1.2.5 (2 studies, 531 participants): RR 0.73, 95% CI 0.61 to 0.88; I^2 = 0%), but not in patients with AKI related to non-surgical causes (Analysis 1.2.6 (3 studies, 1871 participants): RR 0.94, 95% CI 0.73 to 1.20; I^2 = 76%).

The heterogeneity observed in subgroup analyses could be explained by AKI aetiology (test for subgroup differences: Chi^2 = 9.56; P = 0.09; I^2 = 47.7%). When the post-surgery AKI group

was removed from the analysis, I^2 = 0% (test for subgroup differences: Chi^2 = 1.96, P = 0.74).

We downgraded the quality of evidence from high to low due to inconsistency and imprecision on the following subgroup analyses: patients with and without sepsis, patients with high and low SOFA cardiovascular score and patients with non-surgical AKI. High quality of evidence was found for the subgroup of patients with AKI related to surgery (Summary of findings 2).

Sensitivity analysis

The sensitivity analysis was performed excluding studies by risk of bias and large studies. When the analysis was developed taking risk of bias into account we observed that Saudan 2006 contributed to heterogeneity, and when excluded, heterogeneity was not significant (P = 0.63; I^2 = 0%). The reason for exclusion was significant imbalance in the severity of illness observed between treatment arms. The effect of high intensity on mortality changed, but the direction of effects remained constant. We found no changes in heterogeneity when the study with larger sample size was excluded. Data on death or non-recovery at 90 days was not available.

Recovery of kidney function

Five studies reported information on recovery of kidney function (in all patients and among survivors). Studies varied in reporting of kidney recovery timing: 90 days after randomisation (RENAL Study 2006; Saudan 2006); 28 days (RENAL Study 2006; Saudan 2006; Tolwani 2008); at hospital discharge (Bouman 2002;Tolwani 2008); or 15 days after cessation of CRRT (Ronco 2000a).

Overall, there was no significant difference between intensive versus less intensive CRRT in the numbers of patients who were free of RRT after CRRT discontinuation (Analysis 1.3.1 (5 studies, 2402 participants): RR 1.12, 95% CI 0.91 to 1.37; I^2 = 71%). There was substantial heterogeneity among studies. We downgraded the quality of evidence from high to low due to inconsistence and imprecision.

Similarly there was no significant difference between intensive versus less intensive CRRT on recovery of kidney function among survivors who discontinued CRRT at day 30 (Analysis 1.3.2 (5 studies, 1415 participants): RR 1.03, 95% CI 0.96 to 1.11; I^2 = 69%) or at day 90 (Analysis 1.3.3 (3 studies, 988 participants): RR 0.98, IC 95% 0.94 to 1.01, I^2 = 0%). We downgraded the quality of evidence from high to low due to inconsistency and indirectness and rated as moderate quality of evidence, due to indirectness, respectively (Summary of findings for the main comparison)

Subgroup analysis and investigation of heterogeneity

There was evidence of significant heterogeneity in the magnitude of the effect among the included studies that measured recovery of kidney function at different times in relation to randomisation.

To assess heterogeneity among participants, we performed prespecified subgroup analyses by age, gender, fluid overload (≤ 10% and > 10% in body weight in relation to baseline), according to AKI aetiology and severity of illness. Only data for AKI aetiology were available. The effect of AKI aetiology was assessed using subgroups: patients with AKI predominantly related to surgical causes and patients with AKI related to non-surgical causes. Compared to less intensive CRRT, intensive CRRT increased recovery of kidney function in patients with post-surgical AKI (Analysis 1.4.1 (2 studies, 531 participants): RR 1.27, 95% CI 1.05 to 1.53, P = 0.01, I^2= 0%), but there were no difference on recovery of kidney function in patients with AKI related to non-surgical causes (Analysis 1.4.2 (3 studies, 1870 participants): RR 1.12, 95% CI 0.73 to 1.71, P = 0.61, I^2= 82%). There was no heterogeneity between groups (test for subgroup differences: Chi^2 = 0.27, P = 0.60, I^2 = 0%).

Sensitivity analysis

There was evidence of heterogeneity in recovery of kidney function up to 30 days after discontinuation of CRRT (I^2 = 69%). We performed sensitivity analyses to explore the above listed factors on the effect size. Few data were available. Sensitivity analysis was performed excluding studies with high risk of bias and those with large sample sizes. When the analysis was developed taking risk of bias into account, we observed that Ronco 2000a contributed to heterogeneity. When excluded, heterogeneity was not significant (P = 0.63; I^2 = 0%). Ronco 2000a included a non-validated outcome (kidney recovery 15 days after cessation of CRRT) and enrolled patients with high incidence of post-surgical AKI, which may have contributed to a better prognosis on recovery of kidney function. The effect of intensive CRRT remained constant and the direction of effects did not change.

Length of stay

RENAL Study 2006 and Tolwani 2008 compared the effects of intensity of CRRT on length of stay. There were no significant differences between intensive and less intensive CRRT on the number of days in hospital (Analysis 1.5.1 (2 studies, 1665 participants): MD -0.23 days, 95% CI -3.35 to 2.89; I^2 = 8%) and the number of days in ICU (Analysis 1.5.2 (2 studies, 1665 participants): MD -0.58 days, 95% CI -3.73 to 2.56, I^2 = 19%). We downgraded the quality of evidence from high to low due to substantial imprecision and risk of bias.

Metabolic control

There was no significant difference between intensive and less intensive CRRT on the numbers of patients who normalised metabolic acidosis (Analysis 1.6.1 (1 study, 115 participants): RR 1.05, 95% CI 0.73 to 1.51). We rated this as moderate quality evidence due to imprecision.

Adverse events

The effects of intensity of CRRT on adverse events were reported in three studies (Bouman 2002; RENAL Study 2006; Saudan 2006). Intensive CRRT increased the risk of hypophosphataemia (Analysis 1.7.2 (1 study, 1441 participants): RR 1.21, 95% CI 1.11 to 1.31) compared to less intensive CRRT. We rated this as high quality evidence.

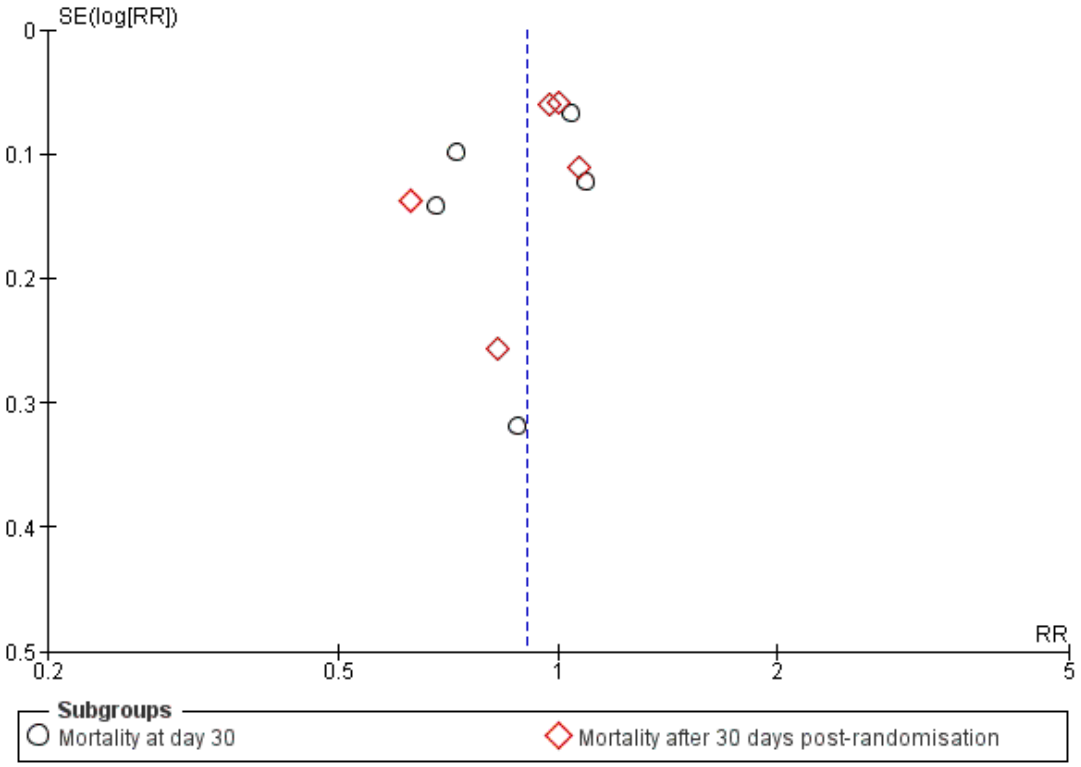
There were no significant differences between intensive and less intensive CRRT on the numbers of patients who experienced adverse events (Analysis 1.7.1 (3 studies, 1753 participants): RR 1.08, 95% CI 0.73 to 1.61; I^2 = 16%), hypokalaemia (Analysis 1.7.3 (1 study, 1455 participants): RR 0.96, 95% CI 0.80 to 1.15), arrhythmia (Analysis 1.7.4 (1 study, 1463 participants): RR 0.92, 95% CI 0.80 to 1.06), and bleeding (Analysis 1.7.5 (3 studies, 1775 participants): RR 0.78, 95% CI 0.27 to 2.24; I^2 = 0%). We downgraded the quality of evidence from high to moderate due to imprecision and for the last outcome we rate as low quality evidence due to substantial imprecision (Summary of findings for the main comparison).

Fluid balance and costs of CRRT were not reported in any of the included studies.

Evaluation of publication bias

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

Figure 4. Funnel plot of comparison: 1 High Intensity versus less intensive CRRT, outcome: 1.1 Mortality



ADDITIONAL SUMMARY OF FINDINGS [Explanation]

Intensive versus less intensive CRRT for AKI: subgroups

Patient or population: patients with AKI who need CRRT
Settings: ICU
Intervention: Intensive CRRT
Comparison: Less intensive CRRT

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Standard dose	High dose				
Mortality: patients with sepsis Follow-up: mean 28 days	**Study population**		**RR 0.94** (0.69 to 1.27)	966 (5)	⊕⊕◯◯ **low**[1,2]	
	524 per 1000	**492 per 1000** (361 to 665)				
	Moderate					
	618 per 1000	**581 per 1000** (426 to 785)				
Mortality: patients without sepsis Follow-up: mean 28 days	**Study population**		**RR 0.89** (0.69 to 1.15)	1216 (4)	⊕⊕◯◯ **low**[1,2]	
	465 per 1000	**414 per 1000** (321 to 535)				
	Moderate					
	564 per 1000	**502 per 1000** (389 to 649)				

Mortality: patients with AKI related to cardiac or general surgery Follow-up: mean 21 days	**Study population**		**RR 0.73** (0.61 to 0.88)	531 (2)	⊕⊕⊕⊕ **high**
	505 per 1000	**368 per 1000** (308 to 444)			
	Moderate				
	459 per 1000	**335 per 1000** (280 to 404)			
Mortality: patients with AKI not related to surgery Follow-up: mean 30 days	**Study population**		**RR 0.94** (0.73 to 1.20)	1871 (3)	⊕⊕◯◯ **low**[1,2]
	414 per 1000	**389 per 1000** (302 to 497)			
	Moderate				
	550 per 1000	**517 per 1000** (402 to 660)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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/s; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] inconsistency: due to substantial heterogeneity (I^2 values ranged from 73% to 78%)
[2] imprecision: due to wide CI which crossed the threshold for clinically meaningful effects

DISCUSSION

Summary of main results

Our systematic review and subsequent meta-analysis examines the effect of different intensities of CRRT on mortality, kidney recovery function and adverse events among 3185 critically ill patients with AKI. Most of the included studies were assessed at low or unclear risk of bias for all domains. Within the intensity ranges assessed, more intensive CRRT did not demonstrate beneficial effects on mortality at different time points post randomisation (day 30 or after 30 days) and kidney recovery function (in all patients and among survivals at 30 and 90 days before randomisation) compared with less intensive therapy. The overall estimated effects on these outcomes are not statistically significant; the confidence intervals are sufficiently wide to include clinically benefits and harm (imprecision), with high level of heterogeneity (inconsistency). Treatment with more intensive CRRT increased the risk of hypophosphataemia, although it did not increase other adverse events when compared to less intensive CRRT. All results (except hypophosphataemia) were imprecise because the confidence intervals were wide which crossed the threshold for clinically meaningful effects.

An important limitation of this systematic review was the substantial heterogeneity found in the main results as mortality at day 30 or after 30 days (I^2 = 75% and I^2 = 65% respectively) and recovery of kidney function in all patients and among survivals at 30 (I^2 = 71% and I^2 = 69% respectively). However, there was no heterogeneity identified for recovery of kidney function at 90 days (I^2 = 0%). We explored this heterogeneity by two prespecified clinical subgroup analyses; severity of acute illness (patients with and without sepsis and high and low SOFA cardiovascular scores) and by aetiology of AKI. We found that in patients with surgery-acquired AKI, intensive CRRT reduced mortality risk at day 30 compared to those patients with non-surgically-acquired AKI. Therefore, AKI aetiology was identified as a source of heterogeneity in the size of effect among included studies.

More intensive CRRT had uncertain effects on length of stay, number of days in ICU and number of days in hospital. These results should be interpreted with caution owing to the fact that only two small studies reported these data. Some studies have reported days in hospital and days in ICU but, in patients with a high short-term mortality risk, the interpretation of such results may be misleading given the mortality is a competing end point for length of stay.

Overall completeness and applicability of evidence

See Description of studies; Characteristics of included studies

Six randomised studies (ATN Study 2005; Bouman 2002; RENAL Study 2006; Ronco 2000a; Saudan 2006; Tolwani 2008) evaluated the effect of different intensities of CRRT on survival and recovery of kidney function in critically ill patients with AKI. Two studies (Ronco 2000a; Saudan 2006) favoured more intensive therapy. In contrast, four other studies (ATN Study 2005; Bouman 2002; RENAL Study 2006; Tolwani 2008) have not demonstrated beneficial effects with an increased intensity of therapy on clinical outcomes. These results are consistent with those reported in our review.

Disparity and the heterogeneity found in these results among the studies probably may explained by several factors such as differences in methodological quality of studies, patients characteristics, delivered dialysis dose, and timing of CRRT initiation.

In a study of 425 patients, Ronco 2000a reported a decrease in mortality at day 15 from 59% to 43% with an increased in the intensity from 20 mL/kg/h to 35 or 45 mL/kg/h. We observed some limitations in this study: an absence of detailed description of randomisation and allocation concealment process (limiting the internal validity); a low incidence of patients with AKI-related to sepsis (15%); and a non-validated short-term outcome (limiting the external validity). In Saudan 2006 (206 patients with AKI) there was a 26% reduction in all-cause of mortality at day 90 (from 62% to 36%) with an increase in the intensity of CRRT from 25 mL/kg/h to 45 mL/kg/h. This study has an important imbalance in the severity of illness observed between CVVH treatment arms (limiting the internal validity). Additionally, both studies were unblinded, single-centre studies (limiting the internal and external validity respectively). In contrast, three studies evaluating intensity in continuous therapy, and one study in combined modalities (Intermittent and continuous), did not demonstrate any effect of increased intensity of therapy on survival. Bouman 2002 conducted a small study evaluating both intensity and timing of initiation of CVVH in 106 critical patients with AKI. There were no differences on the survival for either intensities or initiation time. It is interesting to note that the actual delivered therapy in the high-intensity arm was much less than the prescribed intensity. Furthermore, survival was greater than expected (survival at 28 days 69% to 75% in all groups) probably related to a low incidence of patients with AKI-related to sepsis (limiting the external validity). The study was underpowered due to the small sample size. Similarly, Tolwani 2008 evaluated 200 patients with AKI. They found no difference on survival with intensive continuous therapy. This was an unblinded, single-centre study (limiting the internal and external validity respectively). Finally, two large multicentre studies were conducted. In ATN Study 2005, 1124 critically ill patients with AKI were randomised to high-intensity or low-intensity. Within treatment groups, patients were allocated to CVVHDF or SLED and IHD according to cardiovascular SOFA score. In RENAL Study 2006, 1508 patients were randomly assigned to two intensities of CVVHDF (intensive or less intensive). All patients received CRRT as their first mode of RRT; only a small proportion of patients received IHD (7%). Both studies reported no beneficial effect on mortality and recovery of kidney function associated with a more intensive RRT.

There were also differences in the prescribed and delivered doses

of CRRT. In ATN Study 2005, the dose delivered was 89% of that prescribed for higher-intensity treatment, Tolwani 2008 reported a value of 83%, and in RENAL Study 2006 the delivered dose was 84%. For the lower-intensity treatment, the doses delivered were 95% in ATN Study 2005, 85% in Tolwani 2008, and 88% in RENAL Study 2006. In all other studies (Bouman 2002; Ronco 2000a; Saudan 2006) delivered doses were less than 85% of the prescribed doses. The difference between the prescribed and the delivered dose highlights the risk of overestimating the effective delivery of therapy and the need to improve operational measures in CRRT.

Although the analysis included data obtained from a comprehensive and rigorous search, we identified gaps in several areas. The majority of participants of the included studies were adults, limiting the applicability of our finding to children. In general, the incidence of AKI secondary to sepsis is very high in ICU (50% to 60%); however, in two studies it was observed that the majority of patients had post-surgical AKI, and relatively few had sepsis or pre-existing chronic kidney disease, limiting the applicability of our results to general ICU population. Three included studies were single-centre studies, limiting the external validity of the results.

While the urea kinetics remains widely used to measure intensity of RRT in AKI-patients, this approach provides an incomplete assessment of dose of RRT, especially in the critically ill patients with AKI.

An important challenge when examining the evidence of dialysis intensity in patients with AKI is to determine the exact number of patients who received IHD or CRRT in those studies using a combination of both strategies (ATN Study 2005), as well as distinguishing which patients remained dialysis-depend after ICU discharge or received transitory IHD without regard to the original assigned treatment. In view of this, we contacted the authors for more information. The long-term kidney outcomes after hospital discharge among survivors of AKI remain poorly characterised. The studies did not report data on mortality and kidney function recovery in patients with pre-existing chronic kidney disease and with low or intermediate scores of severity of illness. The results on length of stay (days in hospital and in the ICU) and recovery of kidney function should be interpreted with caution, especially when the mortality risk is taken into account.

We are aware that an important aspect to consider in term of efficacy is the timing in which CRRT are indicated. Currently, we are trying to answer this question with a systematic review specified (Fayad 2013a).

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 2011). Our review was based on evidence from six RCTs (3185 participants) that compared different intensities of CRRT in critically ill patients with AKI. The quality of evidence for our main outcomes was drawn from studies assessed at low risk of bias for random sequence generation and allocation concealment processes, incomplete outcome data, intention to treat analysis, selective outcomes reporting, performance bias and other sources of bias; and unclear risk for detection bias.

Data comparing the effect of higher intensity versus lower intensity CRRT on mortality at day 30 or after were obtained from six well-conducted RCTs respectively, but we downgraded the quality of evidence to low, mainly due to inconsistencies (I^2 values of 65% and 75%) and imprecision (CIs included a range of plausible values with clinically important benefits but also included harms). Similarly, we downgraded the quality of evidence to low for recovery of kidney function in all patients and among survivors at day 30 due to inconsistencies (I^2 values of 71% and 69%) and rated as moderate data obtained for recovery of kidney function among survivors at day 90 by 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 intensive versus less intensive CRRT on adverse events were obtained from three well-conducted RCTs, providing treatment effects with clinically important harms; however, we downgraded the quality of evidence to moderate due to imprecision (CIs included both clinically important benefits and harm). One study provided data on hypophosphataemia. We rated this as high quality evidence.

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 for evidence to assess the risk of publication bias was not possible for all outcomes due to the small number of studies available in each meta-analysis (Figure 4).

It was difficult to identify the number of patients who received IHD in the included study using a combination of both therapies (intermittent and continuous), as well also in studies evaluating CRRT intensity, in which patients remained dialysis-dependent after ICU or hospital discharge, many were likely to have transitioned to IHD regardless of the original study-assigned dose of CRRT.

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

Agreements and disagreements with other studies or reviews

Our systematic review in keeping with previous meta-analysis on intensity in CRRT (Negash 2011) or in mixed modality, combining intermittent, sustained and continuous dialysis (Jun 2010; Van Wert 2010), has not found beneficial effects of more intensive RRT with respect to mortality and kidney recovery function in critically ill patients with AKI compared to less intensive therapy. There has been increased interest in recovery of kidney function. Indeed, lack of recovery of kidney function implies the need for long-term dialysis associated with low quality of life. Our review has not demonstrated benefits on recovery of kidney function with intensive therapy. These findings are consistent with four individual RCTs (ATN Study 2005; Bouman 2002; RENAL Study 2006; Tolwani 2008) and do not agree with those reported of two previous RCTs (Ronco 2000a; Saudan 2006). It is important to note that relevant differences on recovery of kidney function between ATN Study 2005 and RENAL Study 2006 were observed (45.2% versus 13.3% of survivors depend on RRT at day 28 respectively). These differences may be due to several factors including different populations, prevalence of intermittent dialysis, pre-existing chronic kidney disease and timing of RRT initiation. A review by Palevsky 2005 on factors affecting kidney recovery following AKI did not recommend either intensities with regard to recovery of kidney function when the mortality risk is taken into account (given that mortality is a competing end point for recovery of kidney function).

The hypothesis that in critically ill patients, especially those with sepsis or systemic inflammatory responses, could benefit from an intensive CRRT was proposed by several researchers. It is interesting to note that we did not find benefit from higher intensity CRRT in this subgroup of patients in our review. These results were consistent with previous meta-analysis (Jun 2010; Van Wert 2010). Additionally, previous reviews explored the effect of high volume haemofiltration (HVHF) specifically in critically ill patients with severe sepsis or septic shock in an ICU setting (Borthwick 2013; Clark 2014; Lehner 2014). These reviews applied different thresholds for HVHF: Borthwick 2013 defined HVHF as > 35 mL/kg/h, while more recent reviews define HVHF as >50 mL/kg/h (Clark 2014) and HVHF and pulse high volume haemofiltration (PHVHF) as 85 mL/Kg/h (Lehner 2014). These reviews included studies we excluded from our review due to the very-high intensity applied (Boussekey 2008; IVOIRE Study 2013; Sanchez 2010b; Zhang 2012) or no requirement of AKI for enrolment (Jiang 2005) These reviews found insufficient evidence of a therapeutic benefit for routine use of HVHF for septic AKI.

AUTHORS' CONCLUSIONS

Implications for practice

With available data of included RCTs, more intensive CRRT (range between 35 to 48 mL/kg/h) demonstrated no beneficial effects on mortality or recovery of kidney function, however there was an increased risk of hypophosphataemia compared to less intensive therapy (range between 20 to 25 mL/kg/h). The absence of high quality evidence of efficacy and the possibility of increased adverse events does not support the routine use of high intensity CRRT in this group of patients. However, in patients with postsurgical AKI, high intensity CRRT appears to reduce the risk of death.

These results do not minimise the importance of the intensity in continuous treatment of critically ill patients with AKI. Minimal standards for the delivered dialysis dose of therapy appear to have been identified (KDIGO 2012). There is evidence to suggest that the mortality in these high-risk populations will be substantially altered by improvements in the delivery kidney support.

Our results are likely to have implications for clinical practice in countries (Europe; New Zealand and Australia) where CRRT is now the preferred form of RRT in the ICU (Uchino 2005). However, in clinical practice, haemodynamically unstable patients are commonly managed using CRRT and haemodynamically stable patients are generally treated using IHD; frequently these patients receive both modalities over the course of their illness as their haemodynamic status change.

Implications for research

Given the persistently high mortality rate among patients with AKI, it would be important to accurately determine the effect of intensity of CRRT on mortality particularly in patients with postsurgical AKI. In view of the inconsistencies observed in the main outcomes and the inability to assess all possible causes of heterogeneity, it would be important to perform pooled analyses of individual patient data from all completed studies to deal with heterogeneity issues. Such an initiative (a patient-level meta-analysis of all of the intensity of RRT studies) is being conducted by the George Institute for Global Health in Australia.

Optimal timing of CRRT initiation during therapy needs to be rigorously evaluated. It would be important to perform pooled analysis of individual patient data from all completed studies to deal with heterogeneity issues.

There is also a need to investigate other strategies that can be implemented alone or concurrently to CRRT for the treatment of AKI.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

ATN Study 2005

Methods	• Study design: prospective, parallel RCT • Study duration: November 2003 to July 2007
Participants	• Setting: multicentre (27 ICU) • Country: USA • Critically ill patients aged ≥ 18 years with AKI due to ATN who require RRT defined as a) Clinical setting of Ischaemic or nephrotoxic injury, b) oliguria (average urine output ≤ 20 mL/hour) for > 24 hours or an increase in SCr of ≥ 2mg/dL (177 μmol/L) in males or ≥ 1.5 mg/dL (133 μmol/L) in females over a period of ≤ 4 days; receiving care in a critical care unit); 1 non-renal organ failure (SOFA score ≥ 2) or the presence of sepsis; patient/surrogate willing to provide informed consent • Number: treatment group (563); control group (561) ○ CRRT treatment: 783 patients (69.7%) • Mean age ± SD (years): treatment group (59.6 ±15.3); control group (59.7 ± 15.2) • Sex (M/F): treatment group (409/154); control group (384/176) • Exclusion criteria: baseline SCr > 2 mg/dL (177 μmol/L) in males, > 1.5 mg/dL (133 μmol/L) in females; AKI clinically believed to be due to an aetiology other than ATN; more than 72 hours since meeting both of the following conditions a) fulfilment of the definition of AKI, b) BUN > 100 mg/dL (36 mmol/L); ≥ 1 HD treatment or more than 24 hours since starting CRRT; prior kidney transplant; pregnancy; prisoner; weight > 128.5 kg; non-candidacy for RRT; moribund state; patient not expected to survive 28 days because of underlying terminal chronic medical condition; comfort-measures-only status; participation in a concurrent interventional study; patient/surrogate refusal; physician refusal
Interventions	• Modalities: IHD, CVVHDF, SLED • Haemofilter: cellulose triacetate or synthetic membranes • Replacement fluid: pre-dilution mode • Anticoagulation: heparin, citrate, other Treatment group • Intensive management strategy ○ If haemodynamically stable ◇ IHD 6 times/week (target delivered Kt/V ~ 1.2 to 1.4/treatment) ○ If haemodynamically unstable ◇ CVVHDF at 35 mL/kg/h; or ◇ SLED, 6 times/week (target delivered Kt/V ~ 1.2 to 1.4/treatment) Control group • Conventional management strategy ○ If haemodynamically stable ◇ IHD 3 times/week (target delivered Kt/V ~ 1.2 to 1.4/treatment) ○ If haemodynamically unstable ◇ CVVHDF at 20 mL/kg/h; or ◇ SLED, 3 times/week (target delivered Kt/V ~ 1.2 to 1.4/treatment) Co-interventions • Not reported

ATN Study 2005 (*Continued*)

Outcomes	Primary outcomes • Mortality from any cause at day 60 Secondary outcomes • Hospital mortality • 1 year mortality • Recovery of kidney function by day 28 Tertiary endpoints • Duration of RRT • ICU length of stay • Hospital length of stay • Discharge to "home" off of dialysis by day 60 • SOFA scores at days 1 to 14, 21 and 28 Economic analysis • RRT-specific cost of care • Global cost of care • Patient utility
Notes	

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
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement (for kidney recovery was unclear risk but for mortality 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	Per cent followed: 99.55%
Selective reporting (reporting bias)	Low risk	The study reported mortality, kidney function recovery and adverse events
Other bias	Low risk	Funding sources were reported

Bouman 2002

Methods	• Study design: parallel RCT • Study duration: May 1998 to March 2000
Participants	• Setting: 2 centres • Country: The Netherlands • Patients with circulatory and respiratory insufficiency and early AKI who need CRRT; CrCl < 20 mL/min, and oliguria < 180 mL/6 h despite fluid resuscitation; circulatory support and furosemide; early timing: < 12 h inclusion; late timing: BUN > 40 mmol/L or severe pulmonary oedema • Number: treatment group 1 (35); treatment group 2 (35); control group (36) • Mean age ± SD (years): treatment group 1 (68 ± 13); treatment group 2 (70 ± 10) ; control group (67 ± 13) • Sex (M/F): treatment group 1 (21/14); treatment group 2 (20/15); control group (23/13) • Exclusion criteria: pre-existing kidney disease with CrCl of 30 mL/min; AKI caused by permanent occlusion or surgical lesion of the renal artery; glomerulonephritis, interstitial nephritis, or vasculitis; postrenal obstruction; CHILD class C liver cirrhosis; AIDS with a CD4 count of 0.05 109/L; non-witnessed arrest with Glasgow Coma Score 5; haematologic malignancy with neutrophil 0.05 x 10^9/L; no haemofiltration machine free for use at the moment of inclusion
Interventions	• Modality: CVVH • Haemofilter: cellulose triacetate hollow-fibre • Replacement fluid: post-dilution mode with bicarbonate solution • Anticoagulation: heparin or nadroparin Treatment group 1 • Early + high volume haemofiltration group ○ Treatment started within 12 h after time of inclusion, and the ultrafiltration flow rate was high (prescribed dose > 72 L/d and delivered dose 48.2 mL/kg/h) Treatment group 2 • Early + low-volume haemofiltration group ○ Treatment started within 12 h after time of inclusion, and the ultrafiltration flow rate was low (prescribed dose 24 to 36 L/d and delivered dose 19 to 20 mL/kg/h) Control group • Late + low-volume haemofiltration group ○ Treatment started when the patient fulfilled the conventional criteria for RRT: urea level 40 mmol/L, potassium 6.5 mmol/L or severe pulmonary oedema, and the ultrafiltration flow rate was low (24 to 36 L/d and delivered dose 19 to 20 mL/kg/h) Co-interventions • Not reported
Outcomes	Primary outcomes • Mortality at day 28 • Recovery of kidney function Secondary outcomes • ICU survival • Hospital survival • Duration of mechanical ventilation • Length of ICU stay • Length of hospitalisation

Bouman 2002 (*Continued*)

Notes		

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients randomly assigned to the treatment dosage 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 mortality 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	No incomplete data were reported
Selective reporting (reporting bias)	Low risk	The study reported mortality, kidney function recovery and adverse events
Other bias	Unclear risk	Insufficient information to permit judgement

RENAL Study 2006

Methods	• Study design: prospective, parallel RCT • Study duration: December 2005 to November 2008
Participants	• Setting: 35 ICU • Countries: Australia and New Zealand • Critically ill AKI patients who need CRRT; oliguria (urine output < 100 mL in 6 h period) unresponsive to fluid resuscitation measures; potassium > 6.5 mmol; severe acidaemia pH < 7.2/L; urea nitrogen level > 70 mg/dL or 25 mmol/L; SCr > 3.4 mg/dL or 300 μmol/L; pulmonary oedema • Number: treatment group (722); control group (743) • Mean age ± SD (years): treatment group (64.7 ± 14.5); control group (64.4 ± 15.3) • Sex (M/F): treatment group (474/248); control group (472/271) • Exclusion criteria: patients who had received any previous RRT during the same hospital admission or maintenance dialysis for study; patients with ESKD

RENAL Study 2006 (*Continued*)

Interventions	• Modality: CVVHDF • Qb: 150 mL/min • Haemofilter: polyacrylonitrile hollow-fibre • Replacement fluid: post-dilution mode with bicarbonate solution Treatment group • Higher intensity CRRT ○ Prescribed dose: 40 mL/kg/h of effluent dose (delivered dose 33.4 ± 12.8 mL/kg/h) Control group • Lower intensity CRRT ○ Prescribed dose: 25 mL/kg/h of effluent dose (delivered dose 22 ± 17.8 mL/kg/h) Co-interventions • Not reported
Outcomes	Primary outcomes • Mortality at 90 days Secondary outcomes • Mortality at 28 days; in the ICU; in the hospital • Numbers of days of RRT; in ICU; in hospital; of mechanical ventilation • Number of non-renal organ failures
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Patients were randomly assigned using computer-generated methodology
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
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The outcome measurement was unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow up data
Selective reporting (reporting bias)	Low risk	The study reported mortality, kidney function recovery and adverse events
Other bias	Low risk	Funding sources were reported

Ronco 2000a

Methods	• Study design: prospective, parallel RCT • Study duration: 1994 to September 1999
Participants	• Setting: 2 different ICU in the same hospital • Country: Italy • Critically ill AKI patients who need CRRT; admission to ICU • Number: treatment group 1 (139); treatment group 2 (140); control group (146) • Mean age ± SD (years): treatment group 1 (59 ± 9); treatment group 2 (63 ± 12); control group (61 ± 10) • Sex (M/F): treatment group 1 (77/62); treatment group 2 (80/60); control group (81/65) • Exclusion criteria: not reported

Interventions	• Modality: CVVH
	• Haemofilters: polysulfone hollow-fibre
	• Qb: 120 and 240 mL/min
	• Anticoagulation: systemic heparin
	• Replacement fluid: post-dilution mode with lactate solution
	Treatment group 1
	• Higher intensity CRRT
	  ○ Prescribed dose: 35 mL/kg/h (delivered dose 33.5 mL/kg/h)
	Treatment group 2
	• Higher intensity CRRT
	  ○ Prescribed dose: 45 mL/kg/h (delivered dose 42.5 mL/kg/h)
	Control group
	• Lower intensity CRRT
	  ○ Prescribed dose: 20 mL/kg/h (delivered dose 19 mL/kg/h)
	Co-interventions
	• Not reported

Outcomes	Primary outcome • Survival at day 15 after discontinuation of CVVH Secondary outcomes • Recovery of kidney function 15 days after discontinuation of CVVH • Adverse events: clinical and technical complications
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomly assigned using computer-generated methodology
Allocation concealment (selection bias)	Low risk	Central allocation process

Ronco 2000a (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome measurement unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow up
Selective reporting (reporting bias)	Low risk	Reported mortality, kidney function recovery and adverse events
Other bias	Unclear risk	Insufficient information to permit judgement

Saudan 2006

Methods	• Study design: prospective, parallel RCT • Time frame: October 2000 to December 2003
Participants	• Setting: medical and surgical ICU, University Hospital • Country: Switzerland • Critically ill patients with AKI who need CRRT; AKI cause was mostly medical • Number: treatment group (102); control group (104) • Mean age ± SD (years): treatment group (65 ± 12); control group (62 ± 15) • Sex (M/F): treatment group (65/37); control group (57/47) • Exclusion criteria: Pre-renal failure; post-renal failure; ESKD; patients on ACEi
Interventions	• Modalities: CVVHDF and CVVH • Haemofilters: polyacrylonitrile hollow-fibre • Qb: 100 to 125 mL/min • Replacement fluid: pre-dilution mode with bicarbonate or lactate solution • Anticoagulation: heparin Treatment group • Higher intensity CRRT ○ CVVHDF ◇ Prescribed dose: 42 mL/kg/h Control group • Lower intensity CRRT ○ CVVH ◇ Prescribed dose: 25 mL/kg/h
Outcomes	Primary outcome • Survival at days 28 and 90 Secondary outcomes • Recovery of kidney function

Saudan 2006 (*Continued*)

	• Length of ICU stay
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomly assigned using computer-generated methodology in blocks of four and six patients
Allocation concealment (selection bias)	Unclear risk	Allocation was appropriate (sealed opaque envelopes). However, the table 1 showed a significant imbalance in the severity of illness observed between treatment arms
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome measurement unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts or losses to follow up
Selective reporting (reporting bias)	Low risk	Reported mortality, kidney function recovery and adverse events
Other bias	Unclear risk	Insufficient information to permit judgement

Tolwani 2008

Methods	• Study design: prospective, parallel RCT • Study duration: August 2003 to March 2006
Participants	• Setting: University of Alabama (ICU) • Country: USA • ≥ 18 years; critically ill patients with AKI who need CRRT; AKI was mostly medical-volume overload despite diuretics; oliguria (urine output < 200 mL/12 h) despite fluid resuscitation and diuretics; anuria (urine output < 50 mL/12 h); azotaemia (BUN ≥ 80 mg/dL); hyperkalaemia (K ≥ 6.5 mmol/L); SCr increase > 2.5 mg/dL from normal values or a sustained rise in SCr ≥ 1 mg/dL over baseline • Number: treatment group (100); control group (100) • Mean age ± SD (years): treatment group (56 ± 16); control group (62 ± 15) • Sex (M/F): treatment group (59/41); control group (57/43)

	• Relevant health status: critically ill patients with AKI who need CRRT • Exclusion criteria: previous IHD treatment; 24 h CRRT at time of enrolment; weighed > 125 or < 50 kg (limitations of machine); SKD

Interventions	• Modality: CVVHDF
	• Haemofilters: polyacrylonitrile hollow-fibre
	• Qb: 100 to 125 mL/min
	• Replacement fluid: pre-dilution mode
	• Anticoagulation: heparin or no anticoagulation
	Treatment group
	• Higher intensity CRRT
	  ○ Prescribed dose: 35 mL/kg/h
	Control group
	• Lower intensity CRRT
	  ○ Prescribed dose: 25 mL/kg/h
	Co-interventions
	• Not reported

Outcomes	Primary outcome • Survival in ICU discharge or 30 day Secondary outcomes • ICU survival • Hospital survival • ICU kidney recovery • Hospital kidney recovery • ICU length of stay • Hospital length of stay
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Patients were randomly assigned using computer-generated methodology (1:1 ratio between treatment dosages)
Allocation concealment (selection bias)	Low risk	Treatment assignments were kept in numbered, sealed 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
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome measurement unlikely to be influenced by lack of blinding

Incomplete outcome data (attrition bias) All outcomes	Low risk	Per cent followed: 100%
Selective reporting (reporting bias)	Low risk	Reported mortality, kidney function recovery and adverse events
Other bias	Low risk	Funding sources were reported

ACEi - angiotensin-converting enzyme inhibitors; AIDs - acquired immune deficiency syndrome; AKI - acute kidney injury; ATN - acute tubular necrosis; BUN - blood urea nitrogen; CrCl - creatinine clearance; CRRT - continuous renal replacement therapy; CVVH - continuous venovenous haemofiltration; CVVHDF - continuous venovenous haemodiafiltration; HD - haemodialysis; ICU - intensive care unit/s; IHD - intermittent haemodialysis; M/F - male/female; Qb - extracorporeal blood flow; RCT - randomised controlled trial; RRT - renal replacement therapy; SCr - serum creatinine; SD - standard deviation; SLED - sustained low-efficiency dialysis; SOFA - Sequential Organ Failure Assessment

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

Study	Reason for exclusion
Boussekey 2008	Different intensity-arms treatment; control arm was not within the pre-specified range according to protocol: low volume HF (35 ml/kg/h) versus high volume HF (65 ml/kg/h); small sample size (< 20 participants)
Brause 2003	Not RCT
Cole 2002	Compared continuous dialysis therapy versus no haemofiltration
Ghani 2006	Outcomes not relevant for this review; intensity of CRRT was not assessed
HEROICS Study 2015	36% of patients in the control arm did not receive CRRT
IVOIRE Study 2013	Different intensity arms treatment; control arm is not within the pre-specified range according to protocol: standard volume HF (35 mL/kg/h) versus high volume HF (70 mL/kg/h)
Jiang 2005	Different inclusion criteria; included patients with severe pancreatitis, but AKI was no obligatory condition for enrolment; AKI was observed in only 6 (16%) patients
NCT01191905	Different intensity arms treatment; less intensive arm is not within the pre-specified range according to protocol: standard volume HF (40 mL/kg/h) versus high volume HF (80 mL/kg/h)
NCT01251081	Different intensity arms treatment; the control arm is not within the pre-specified range according to protocol: high volume HF (50 mL/kg/h) versus extra high volume HF (85 mL/kg/h)
Payen 2009	Outcomes not relevant for this review; intensity of CRRT was not assessed

(*Continued*)

Sanchez 2010b	Different intensity arms treatment; control dose arms are not within the pre-specified range according to protocol: high volume HF (35 mL/kg/h) versus very high volume HF (> 55 mL/kg/h)
Vesconi 2009	Compared CRRT versus IHD
Zha 2012	Not RCT
Zhang 2012	Different intensity arms treatment; the control arm is not within the pre-specified range according to protocol: high volume HF (50 mL/kg/h) versus extra high volume HF (85 mL/Kg/h)

CRRT - continuous renal replacement therapy; HF - haemofiltration; IHD - intermittent haemodialysis; RCT - randomised controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

NCT01560650

Methods	• Study design: RCT • Study duration: March 2011 to August 2015 (final data collection date for primary outcome measure)
Participants	• Setting: Guangdong General Hospital • Country: China • CRRT indications for AKI (RIFLE criteria) patients with cardiac surgery • Number: 211 • Age: ≥ 18 years • Exclusion criteria: < 18 years; CKD; dialysis history, to leave the ICU patients with AKI, CKD; all causes kidney damage (pathology, haematuria, and radiographic abnormalities) ≥ 3 months or GFR < 60 mL/min for 3 months or more
Interventions	Treatment group • High dose (35 mL/kg/h) CVVH Control group • Low dose (25 mL/kg/h) CVVH
Outcomes	Primary outcomes • Death from any cause within 14, 28 and 90 days after randomisation Secondary outcomes • Kidney outcome of survivors 14, 28 and 90 days after randomisation
Notes	• This study is now completed; no study results have been posted (September 2016)

AKI - acute kidney injury; CKD - chronic kidney disease; CRRT - continuous renal replacement therapy; CVVH - continuous venovenous haemofiltration; GFR - glomerular filtration rate; ICU - intensive care unit/s; RCT - randomised controlled trial

DATA AND ANALYSES

Comparison 1. Intensive versus less intensive CRRT

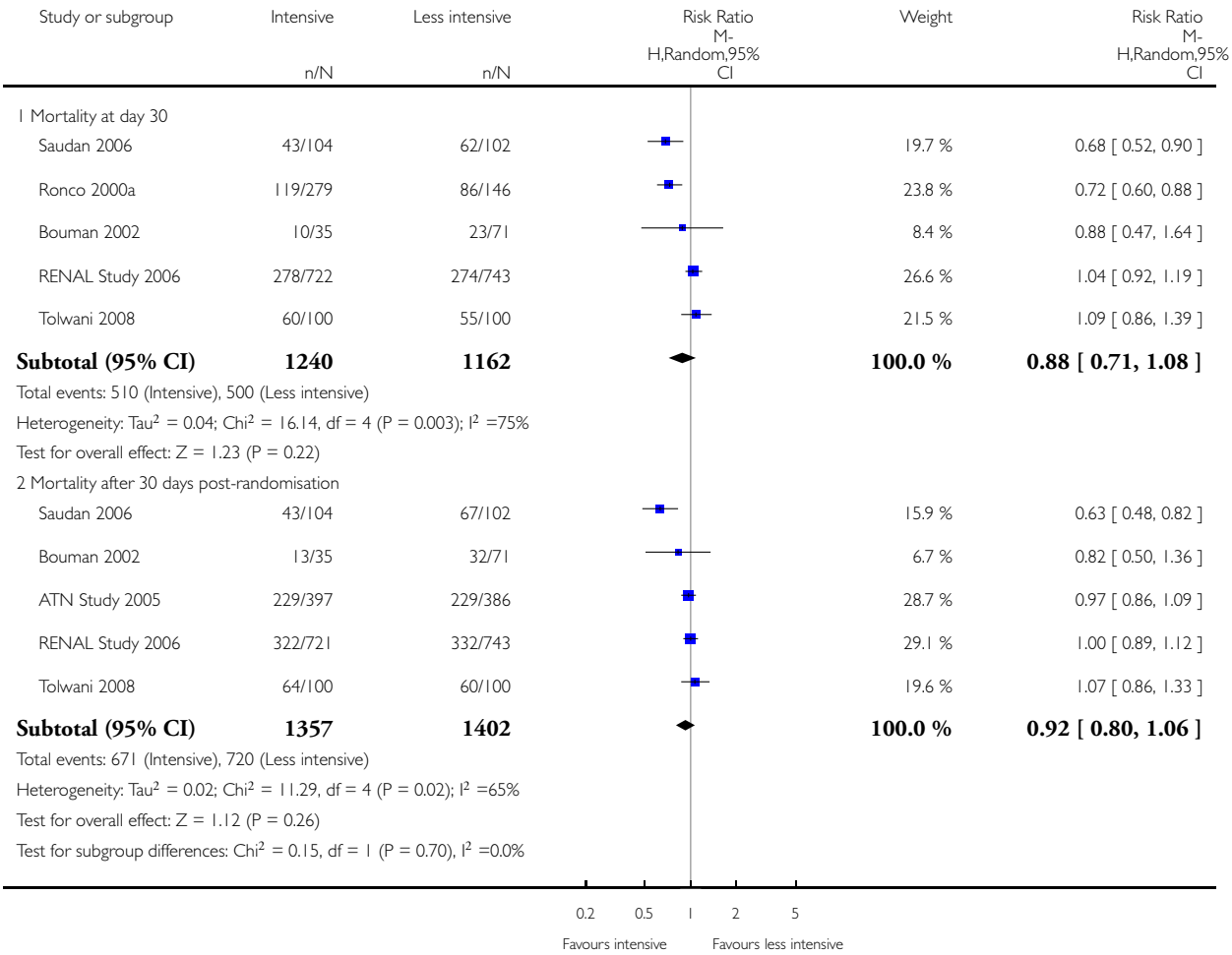
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Mortality at day 30	5	2402	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.71, 1.08]
1.2 Mortality after 30 days post-randomisation	5	2759	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.80, 1.06]
2 Mortality in prespecified groups	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Patients with sepsis	5	966	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.69, 1.27]
2.2 Patients without sepsis	4	1216	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.69, 1.15]
2.3 Patients with SOFA cardiovascular score < 3	1	404	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.71, 1.18]
2.4 Patients with SOFA cardiovascular ≥ 3	1	1056	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.92, 1.18]
2.5 Patients with AKI related to surgical causes	2	531	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.61, 0.88]
2.6 Patients with AKI unrelated to surgical causes	3	1871	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.73, 1.20]
3 Recovery of kidney function	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Free of RRT after discontinuing CRRT	5	2402	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.91, 1.37]
3.2 Free of RRT after discontinuing CRRT at day 30	5	1416	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.96, 1.11]
3.3 Free of RRT after discontinuing CRRT at day 90	3	988	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.94, 1.01]
4 Kidney function recovery in prespecified subgroup	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Patients with AKI related to surgical causes	2	531	Risk Ratio (M-H, Random, 95% CI)	1.27 [1.05, 1.53]
4.2 Patients with AKI related to non-surgical causes	3	1870	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.73, 1.71]
5 Length of stay	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 Days in hospital	2	1665	Mean Difference (IV, Random, 95% CI)	-0.23 [-3.35, 2.89]
5.2 Days in ICU	2	1665	Mean Difference (IV, Random, 95% CI)	-0.58 [-3.73, 2.56]
6 Metabolic control	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.1 Normalised metabolic acidosis	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7 Adverse events	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Patients experiencing adverse events	3	1753	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.73, 1.61]
7.2 Hypophosphataemia	1	1441	Risk Ratio (M-H, Random, 95% CI)	1.21 [1.11, 1.31]
7.3 Hypokalaemia	1	1455	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.80, 1.15]
7.4 Arrhythmia	1	1463	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.80, 1.06]
7.5 Bleeding	3	1775	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.27, 2.24]

Analysis 1.1. Comparison 1 Intensive versus less intensive CRRT, Outcome 1 Mortality.

Review: Intensity of continuous renal replacement therapy for acute kidney injury

Comparison: 1 Intensive versus less intensive CRRT

Outcome: 1 Mortality

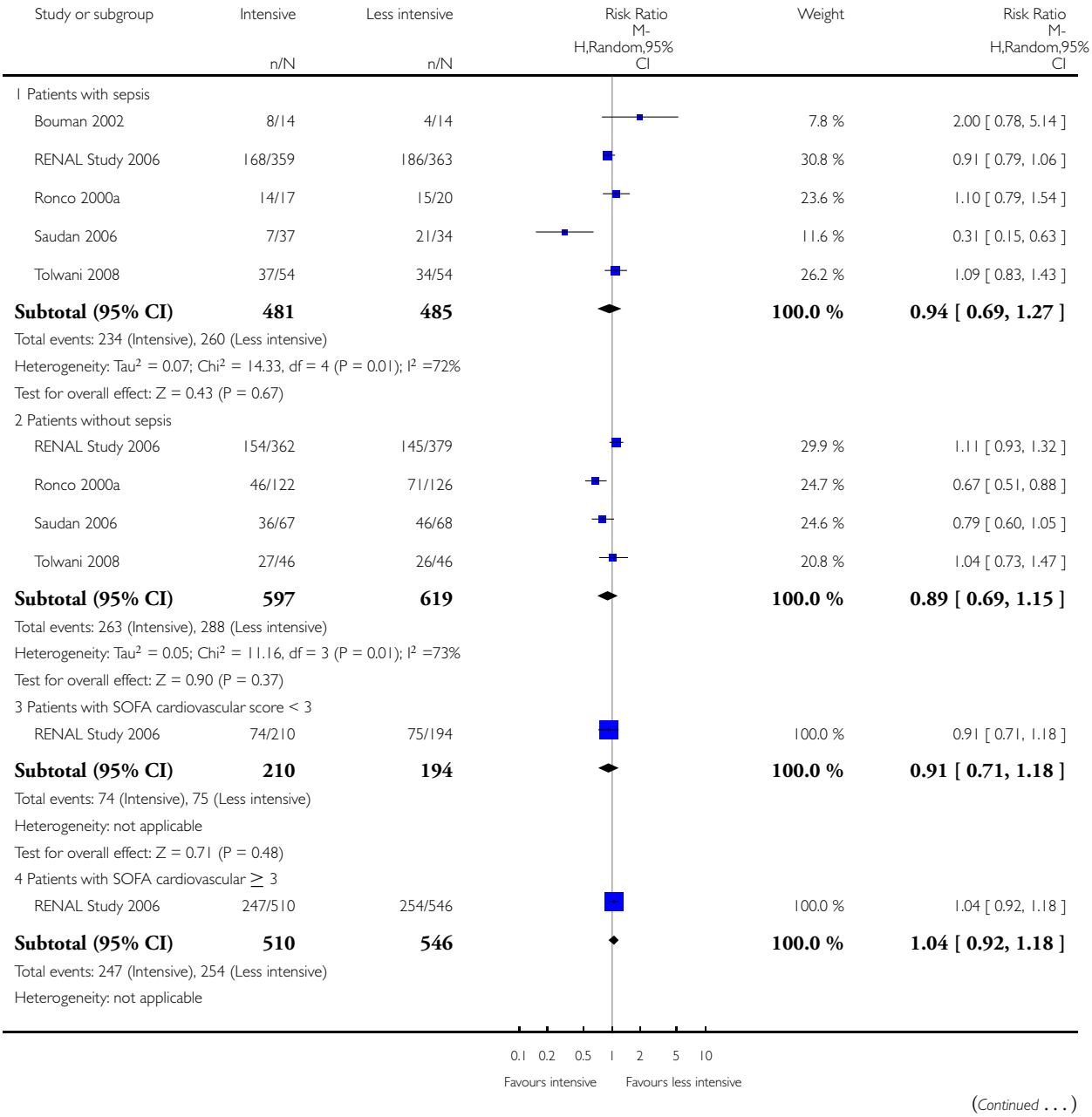


Analysis 1.2. Comparison 1 Intensive versus less intensive CRRT, Outcome 2 Mortality in prespecified groups.

Review: Intensity of continuous renal replacement therapy for acute kidney injury

Comparison: 1 Intensive versus less intensive CRRT

Outcome: 2 Mortality in prespecified groups



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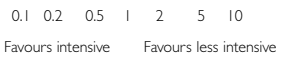
Study or subgroup	Intensive n/N	Less intensive n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Test for overall effect: Z = 0.62 (P = 0.53)					
5 Patients with AKI related to surgical causes					
Bouman 2002	10/36	23/70		8.6 %	0.85 [0.45, 1.58]
Ronco 2000a	119/279	86/146		91.4 %	0.72 [0.60, 0.88]
Subtotal (95% CI)	**315**	**216**		**100.0 %**	**0.73 [0.61, 0.88]**
Total events: 129 (Intensive), 109 (Less intensive)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.22, df = 1 (P = 0.64); I^2 =0.0%					
Test for overall effect: Z = 3.30 (P = 0.00095)					
6 Patients with AKI unrelated to surgical causes					
RENAL Study 2006	278/722	274/743		39.6 %	1.04 [0.92, 1.19]
Saudan 2006	43/104	62/102		28.8 %	0.68 [0.52, 0.90]
Tolwani 2008	60/100	55/100		31.6 %	1.09 [0.86, 1.39]
Subtotal (95% CI)	**926**	**945**		**100.0 %**	**0.94 [0.73, 1.20]**
Total events: 381 (Intensive), 391 (Less intensive)					
Heterogeneity: Tau^2 = 0.04; Chi^2 = 8.32, df = 2 (P = 0.02); I^2 =76%					
Test for overall effect: Z = 0.52 (P = 0.60)					
Test for subgroup differences: Chi^2 = 9.56, df = 5 (P = 0.09), I^2 =48%					

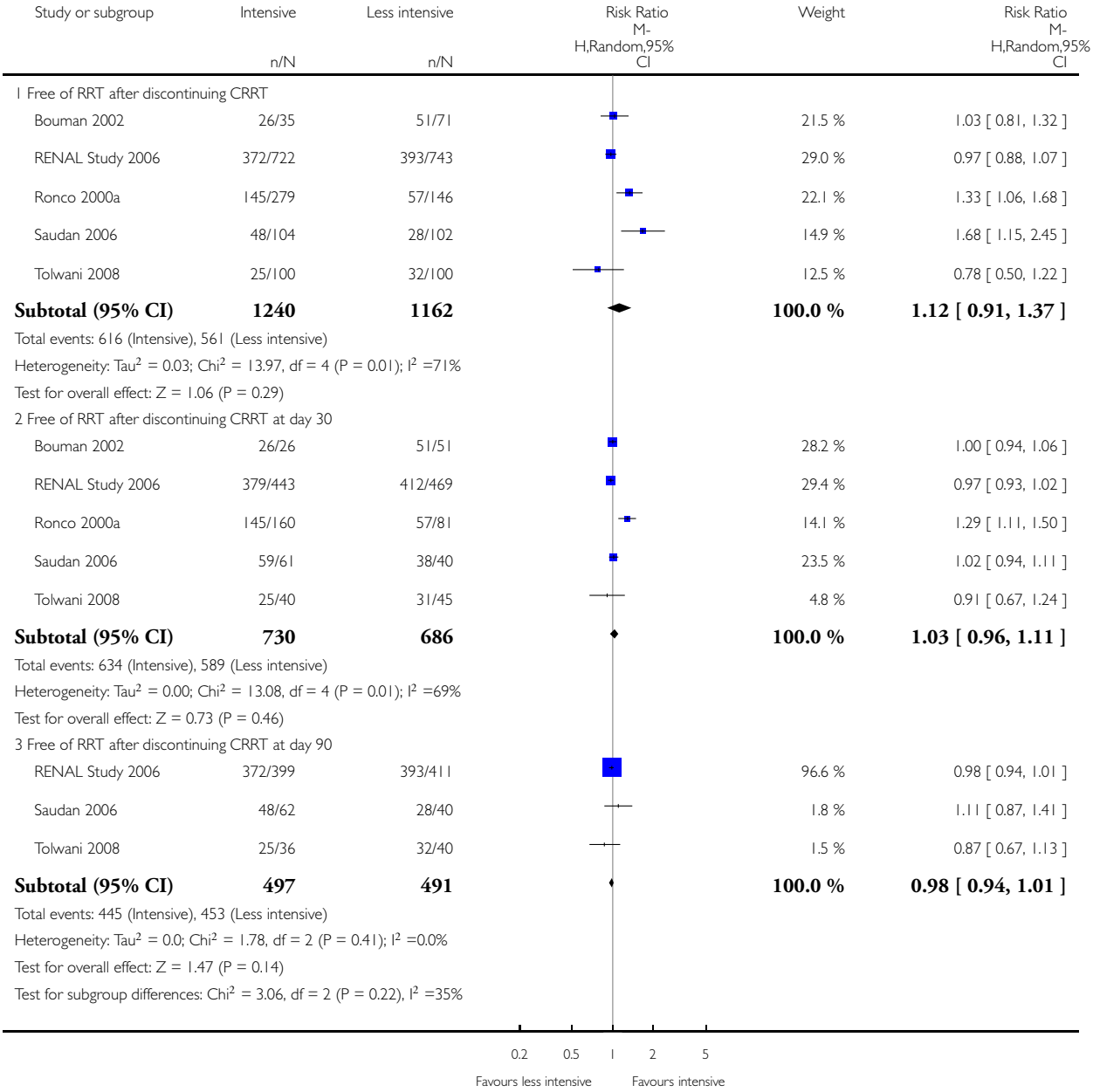


Analysis 1.3. Comparison 1 Intensive versus less intensive CRRT, Outcome 3 Recovery of kidney function.

Review: Intensity of continuous renal replacement therapy for acute kidney injury

Comparison: 1 Intensive versus less intensive CRRT

Outcome: 3 Recovery of kidney function



Analysis 1.4. Comparison 1 Intensive versus less intensive CRRT, Outcome 4 Kidney function recovery in prespecified subgroup.

Review: Intensity of continuous renal replacement therapy for acute kidney injury

Comparison: 1 Intensive versus less intensive CRRT

Outcome: 4 Kidney function recovery in prespecified subgroup

Study or subgroup	Intensive n/N	Less intensive n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Patients with AKI related to surgical causes					
Bouman 2002	22/35	39/71		33.0 %	1.14 [0.82, 1.59]
Ronco 2000a	145/279	57/146		67.0 %	1.33 [1.06, 1.68]
Subtotal (95% CI)	**314**	**217**		**100.0 %**	**1.27 [1.05, 1.53]**
Total events: 167 (Intensive), 96 (Less intensive)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.56, df = 1 (P = 0.46); I^2 =0.0%					
Test for overall effect: Z = 2.44 (P = 0.015)					
2 Patients with AKI related to non-surgical causes					
RENAL Study 2006	372/721	393/743		40.8 %	0.98 [0.88, 1.08]
Saudan 2006	48/104	25/102		30.5 %	1.88 [1.26, 2.81]
Tolwani 2008	25/100	32/100		28.7 %	0.78 [0.50, 1.22]
Subtotal (95% CI)	**925**	**945**		**100.0 %**	**1.12 [0.73, 1.71]**
Total events: 445 (Intensive), 450 (Less intensive)					
Heterogeneity: Tau^2 = 0.11; Chi^2 = 11.17, df = 2 (P = 0.004); I^2 =82%					
Test for overall effect: Z = 0.52 (P = 0.61)					
Test for subgroup differences: Chi^2 = 0.27, df = 1 (P = 0.60), I^2 =0.0%					

Analysis 1.5. Comparison 1 Intensive versus less intensive CRRT, Outcome 5 Length of stay.

Review: Intensity of continuous renal replacement therapy for acute kidney injury

Comparison: 1 Intensive versus less intensive CRRT

Outcome: 5 Length of stay

Study or subgroup	Intensive N	Mean(SD)[days]	Less intensive N	Mean(SD)[days]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Days in hospital							
RENAL Study 2006	722	26 (25.8)	743	25.7 (24.7)		90.0 %	0.30 [-2.29, 2.89]
Tolwani 2008	100	35 (30)	100	40 (39)		10.0 %	-5.00 [-14.64, 4.64]
Subtotal (95% CI)	**822**		**843**			**100.0 %**	**-0.23 [-3.35, 2.89]**
Heterogeneity: Tau^2 = 1.07; Chi^2 = 1.08, df = 1 (P = 0.30); I^2 =8%							
Test for overall effect: Z = 0.14 (P = 0.88)							
2 Days in ICU							
RENAL Study 2006	722	11.8 (14.1)	743	11.8 (14.2)		88.3 %	0.0 [-1.45, 1.45]
Tolwani 2008	100	26 (26)	100	31 (36)		11.7 %	-5.00 [-13.70, 3.70]
Subtotal (95% CI)	**822**		**843**			**100.0 %**	**-0.58 [-3.73, 2.56]**
Heterogeneity: Tau^2 = 2.37; Chi^2 = 1.23, df = 1 (P = 0.27); I^2 =19%							
Test for overall effect: Z = 0.36 (P = 0.72)							
Test for subgroup differences: Chi^2 = 0.02, df = 1 (P = 0.88), I^2 =0.0%							

Analysis 1.6. Comparison 1 Intensive versus less intensive CRRT, Outcome 6 Metabolic control.

Review: Intensity of continuous renal replacement therapy for acute kidney injury

Comparison: 1 Intensive versus less intensive CRRT

Outcome: 6 Metabolic control

Study or subgroup	Intensive n/N	Less intensive n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Normalised metabolic acidosis				
RENAL Study 2006	29/56	29/59		1.05 [0.73, 1.51]

Analysis 1.7. Comparison 1 Intensive versus less intensive CRRT, Outcome 7 Adverse events.

Review: Intensity of continuous renal replacement therapy for acute kidney injury

Comparison: 1 Intensive versus less intensive CRRT

Outcome: 7 Adverse events

Study or subgroup	Intensive n/N	Less intensive n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Patients experiencing adverse events					
Bouman 2002	4/35	15/71		12.9 %	0.54 [0.19, 1.51]
RENAL Study 2006	461/708	396/733		85.1 %	1.21 [1.11, 1.31]
Saudan 2006	1/104	1/102		2.0 %	0.98 [0.06, 15.47]
Subtotal (95% CI)	**847**	**906**		**100.0 %**	**1.08 [0.73, 1.61]**
Total events: 466 (Intensive), 412 (Less intensive)					
Heterogeneity: Tau^2 = 0.05; Chi^2 = 2.38, df = 2 (P = 0.30); I^2 =16%					
Test for overall effect: Z = 0.39 (P = 0.70)					
2 Hypophosphataemia					
RENAL Study 2006	461/708	396/733		100.0 %	1.21 [1.11, 1.31]
Subtotal (95% CI)	**708**	**733**		**100.0 %**	**1.21 [1.11, 1.31]**

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Study or subgroup	Intensive n/N	Less intensive n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Total events: 461 (Intensive), 396 (Less intensive)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.26 (P = 0.000020)					
3 Hypokalaemia					
RENAL Study 2006	168/718	180/737		100.0 %	0.96 [0.80, 1.15]
Subtotal (95% CI)	**718**	**737**		**100.0 %**	**0.96 [0.80, 1.15]**
Total events: 168 (Intensive), 180 (Less intensive)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.46 (P = 0.65)					
4 Arrhythmia					
RENAL Study 2006	240/722	267/741		100.0 %	0.92 [0.80, 1.06]
Subtotal (95% CI)	**722**	**741**		**100.0 %**	**0.92 [0.80, 1.06]**
Total events: 240 (Intensive), 267 (Less intensive)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.12 (P = 0.26)					
5 Bleeding					
Bouman 2002	3/35	10/71		74.4 %	0.61 [0.18, 2.07]
RENAL Study 2006	1/722	0/741		10.9 %	3.08 [0.13, 75.45]
Saudan 2006	1/104	1/102		14.7 %	0.98 [0.06, 15.47]
Subtotal (95% CI)	**861**	**914**		**100.0 %**	**0.78 [0.27, 2.24]**
Total events: 5 (Intensive), 11 (Less intensive)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.90$, df = 2 (P = 0.64); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.46 (P = 0.64)					
Test for subgroup differences: $Chi^2 = 12.91$, df = 4 (P = 0.01), $I^2 = 69\%$					

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 Clinical Trials 3. "acute kidney injury" :ti,ab,kw or "acute renal injury":ti,ab,kw in Clinical Trials 4. "acute kidney insufficiency":ti,ab,kw or "acute renal insufficiency":ti,ab,kw in Clinical Trials 5. "acute tubular necrosis":ti in Clinical Trials 6. (ARI or AKI or ARF or AKF or ATN):ti,ab,kw in Clinical Trials 7. (#1 OR #2 OR #3 OR #4 OR #5 OR #6) 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 Clinical Trials 11. continuous NEAR/2 hemodiafiltration:ti,ab,kw in Clinical Trials 12. continuous NEAR/2 haemodialysis:ti,ab,kw in Clinical Trials 13. continuous NEAR/2 haemodialysis:ti,ab,kw in Clinical Trials 14. (continuous NEXT ultrafiltration):ti,ab,kw in Clinical Trials 15. (continuous NEAR/2 haemofiltration):ti,ab,kw in Clinical Trials 16. (CVVH or CVVHDF or CVVHD or SCUF or CRRT):ti,ab,kw in Clinical Trials 17. (renal replacement therap*):ti,ab,kw in Clinical Trials 18. (#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17) 19. (#7 AND #18)
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$).tw. 5. acute tubular necrosis.tw. 6. (ARI or AKI or ARF or AKF or ATN).tw. 7. or/1-6 8. Renal Replacement Therapy/ 9. exp Renal Dialysis/ 10. (continuous adj3 haemofiltration).tw. 11. (continuous adj3 hemodiafiltration).tw. 12. (continuous adj3 haemodialysis).tw. 13. continuous ultrafiltration.tw. 14. (CVVH or CVVHDF or CVVHD or SCUF or CRRT).tw. 15. renal replacement therap$.tw. 16. or/8-15 17. and/7,16
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

(*Continued*)

	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. renal replacement therap$.tw. 15. or/8-14
LILACS	1. acute kidney failure/ 2. (acute kidney failure or acute renal failure) tw. 3. acute tubular necrosis.tw. 4. or/1-3 5. continuous renal replacement therapy/ 6. (continuous venovenous haemofiltration or continuous venovenous hemofiltration). tw 7. (continuous venovenous haemodiafiltration or continuous venovenous hemodiafiltration).tw. 8. (continuous venovenous haemodialysis or continuous venovenous hemodialysis).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)

(*Continued*)

	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
	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

(*Continued*)

	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 of 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

(*Continued*)

	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias

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
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: none known
- Daniel G Buamscha: none known
- Agustín Ciapponi: none known

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied, Other.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We modified the definitions of intensive and less intensive CRRT according to suggestions of the Editorial Committee and external referees.

'Summary of findings' tables have been incorporated.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Kidney Injury [mortality; *therapy]; Hypophosphatemia [etiology]; Length of Stay; Randomized Controlled Trials as Topic; Recovery of Function; Renal Dialysis [methods]; Renal Replacement Therapy [adverse effects; *methods]

MeSH check words

Humans