High-dose renal replacement therapy for acute kidney injury: Systematic review and meta-analysis

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Objective: To determine the effect of renal replacement therapy dose on mortality and dialysis dependence in patients with acute kidney injury.

Data Sources: MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials to October 2009; PubMed "Related Articles;" bibliographies of included trials; and additional information from trial authors.

Study Selection: Randomized and quasi-randomized, controlled trials in adults with acute kidney injury prescribed high- vs. standard-dose continuous renal replacement therapy (≥30 mL/kg/hr vs. <30 mL/kg/hr), intermittent hemodialysis, or sustained low-efficiency dialysis (daily vs. alternate day, or by target biochemistry).

Data Extraction: Three authors independently selected studies and extracted data on outcomes and study quality. Meta-analyses used random-effects models.

Data Synthesis: Of 5416 citations, 12 trials (n = 3999) met inclusion criteria. Modalities included continuous renal replacement therapy (7 trials), intermittent hemodialysis (3 trials), sustained low-efficiency dialysis (1 trial), and all three (1 trial). Study quality was moderate-high. Meta-analyses found no effect of high-dose renal replacement therapy on mortality (risk ratio, 0.89; 95% confidence interval, 0.77–1.03; 12 trials; n = 3954) or dialysis dependence among survivors (risk ratio, 1.15; 95% confidence interval, 0.92–1.44; 8 trials with events; n = 1743). The effect on mortality was similar (all interaction _p_ values were nonsignificant) in patients with sepsis (risk ratio, 1.02; 95% confidence interval, 0.85–1.23; 9 trials; n = 1786) vs. without sepsis (risk ratio, 0.89; 95% confidence interval, 0.75–1.05; 8 trials; n = 1955), treated exclusively with continuous renal replacement therapy (risk ratio, 0.87; 95% confidence interval, 0.71–1.06; 7 trials; n = 2462) vs. other modalities alone or in combination (risk ratio, 0.92; 95% confidence interval, 0.70–1.21; 5 trials; n = 1492), and in trials with low (risk ratio, 0.96; 95% confidence interval, 0.85–1.09; 6 trials; n = 3475) vs. higher (risk ratio, 0.76; 95% confidence interval, 0.53–1.09; 6 trials; n = 479) risk of bias.

Conclusions: High-dose renal replacement therapy in acute kidney injury does not improve patient survival or recovery of renal function overall or in important patient subgroups, including those with sepsis. (Crit Care Med 2010; 38:1360–1369)

KEY WORDS: acute kidney injury; acute renal failure; renal replacement therapy; renal dialysis; randomized controlled trial; meta-analysis

Severe acute kidney injury (AKI) occurs in approximately 6% of patients admitted to intensive care units (ICUs) (1) and in up to half of patients with septic shock (2). For patients who require renal replacement therapy (RRT), the treatment dose or intensity (referring to small molecule clearance) may affect outcomes. For continuous RRT (CRRT), dose is approximated by the effluent flow rate, whereas for intermittent RRT (most commonly intermittent hemodialysis [IHD]) and sustained low-efficiency dialysis (SLED), treatment dose is typically quantified by the number of sessions (or hours) per week that RRT is applied.

High-dose RRT might benefit critically ill patients with AKI by providing better clearance of toxic molecules or by attenuating the systemic inflammatory response associated with septic shock, pancreatitis, and cardiopulmonary bypass. Several randomized, controlled trials have studied the optimal dose of RRT. A recent systematic review (3) limited to two trials comparing high-dose (≥35 mL/kg/hr) vs. standard-dose (20 mL/kg/hr) continuous venovenous hemofiltration (CVVH) in patients with AKI found that high-dose therapy reduced mortality (risk ratio [RR], 0.74; 95% confidence interval [CI], 0.63–0.88). Since publication of this review, additional randomized, controlled trials have been completed. We therefore conducted an updated systematic review and meta-analysis to de-

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The authors have not disclosed any potential conflicts of interest.

Preliminary results were previously presented in abstract form (Van Wert RJ, Scales DC, Friedrich JO, et al: Optimal dose of renal replacement therapy in acute kidney injury: A meta-analysis. *Crit Care* 2009; 13(Suppl 1): S110).

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termine the effect of high-dose compared to standard-dose RRT in patients with AKI.

MATERIALS AND METHODS

Literature Search

We searched OVID versions of MEDLINE (1950 through October 2009, week 5), EMBASE Classic and EMBASE (1947 through week 44, 2009), and the Cochrane Central Register of Controlled Trials (third quarter, 2009) (see Appendix A for details). We also searched bibliographies of included studies and personal files. We did not impose language restrictions. Two reviewers independently reviewed all citations; the full text of any citation considered potentially relevant by any reviewer was retrieved. We attempted to contact the authors of all included studies for clarification of methods and additional data.

Study Selection

Three unblinded reviewers assessed full-text reports and included studies meeting the following criteria: 1) design: parallel group randomized, controlled or quasi-randomized, controlled (e.g., assigning patients in alternating fashion or by hospital registry number) trial; 2) population: adult patients with AKI by authors' criteria at enrollment; 3) intervention: high-dose compared to standard-dose RRT, with both assigned dose strategies applied using the same RRT modality (CRRT, IHD, or SLED) and for at least 48 hrs; and 4) outcome: all-cause mortality or dialysis dependence among survivors. After discussion and consensus among the investigators, we defined high-dose RRT as ≥30 mL/kg/hr of prescribed effluent flow in CRRT, or six or more sessions per week of 3–4 hrs each (IHD) or 8–12 hrs each (SLED). We defined standard-dose RRT to be <30 mL/kg/hr of prescribed effluent flow (CRRT) or two to four sessions per week (IHD and SLED). We accepted authors' reporting of prescribed CRRT dose without adjustment for the effects of net fluid removal or prefilter replacement fluid on dose (if hemofiltration or hemodiafiltration used). We considered for inclusion: 1) trials with cointerventions if they were applied equally in both groups; 2) trials using different modalities of RRT (i.e., CRRT, IHD, or SLED), provided that high-dose and standard-dose therapies were not delivered by exclusively different modalities; and 3) trials in which RRT was initiated at different times in the high-dose and standard-dose groups, provided that dose clearly differed between the treatment groups throughout the entire study period (for example, differential predialysis serum creatinine or urea targets for intermittent RRT or different effluent flow rates for CRRT). We considered continuous venovenous hemodialysis (CVVHD), CVVH, and continuous venovenous hemodiafiltration (CVVHDF) to be different modes within the same modality (CRRT) and did not exclude trials using different CRRT modes in the high-dose and standard-dose groups. We excluded crossover trials in which all patients received treatment and control interventions in random order.

Data Abstraction and Validity Assessment

Three unblinded reviewers independently abstracted data from included trials, including patient population, RRT methods, outcomes, and study quality. We considered trials to be at low risk for bias if allocation was adequately concealed, <5% of patients were lost to follow-up for mortality, and the trial was not stopped early for benefit. We considered trials to be at higher risk for bias if not all three criteria were present. Disagreements between reviewers at the stages of study selection and data extraction that remained after author contact were resolved by consensus.

Data Analysis

Our primary outcome was all-cause mortality assessed at 90 or 60 days after randomization or, if not available, at hospital discharge, 30 or 28 days after randomization, ICU discharge, or after stopping renal replacement therapy (in descending order of preference). Secondary outcomes included dialysis dependence among survivors (with the same preferred order of time point) and hypotension, as defined by the author. We anticipated that trials would report hypotension differently, precluding a pooled analysis. Pooled analyses included trials (and groups within trials) using CRRT, IHD, and SLED, with dose classified according to prespecified definitions. When a trial had more than one group receiving either high-dose or standard-dose RRT, we combined groups to create one high-dose and one standard-dose group per trial.

We used Review Manager 5.0.22 (The Cochrane Collaboration, Oxford, England) to calculate pooled RRs and 95% CIs for mortality and dialysis dependence and R 2.7.2 (http://www.r-project.org) to create figures. We used random-effects models, which incorporate between-trial heterogeneity and thus generally give wider CIs when heterogeneity is present. We assessed statistical heterogeneity among trials using I^2, the percentage of total variability across studies attributable to heterogeneity rather than chance (4, 5), and used published guidelines for low (I^2 = 25% to 49%), moderate (I^2 = 50% to 74%), and high (I^2 ≥75%) heterogeneity (5). Continuous variables are expressed as mean ± SD, unless otherwise indicated.

We performed subgroup analyses for mortality in patients with sepsis at randomization vs. not, treated exclusively with CRRT vs. not, and enrolled in trials with low vs. higher risk of bias. We also performed a subgroup analysis for dialysis dependence in survivors in patients treated exclusively with CRRT vs. not. We hypothesized that high-dose RRT would be more beneficial in subgroups of patients with sepsis (because of the extreme inflammatory response), treated exclusively with CRRT (because of improved hemodynamic stability), and enrolled in trials at higher risk for bias (in which treatment benefits may be amplified). To test for interaction between dose and subgroup, pooled RRs between subgroups were compared using z tests.

Finally, we anticipated that the timing of initiation of RRT after the onset of AKI might differ between high-dose and standard-dose groups of patients in some trials. We therefore conducted sensitivity analyses for the outcomes of mortality and dialysis dependence in survivors restricted to trials and arms within trials in which patients started assigned therapy at the same time after enrollment. To assess publication bias, we visually examined a funnel plot of study precision vs. effect on mortality for evidence of asymmetry.

RESULTS

Study Flow

Our search strategy yielded 5416 citations (Fig. 1). We retrieved 32 articles for detailed evaluation, of which 20 were excluded (Appendix B). Twelve trials (3999 patients) met criteria for inclusion (6–17). The authors of eight trials provided additional data (7, 9, 10, 12–14, 16, 17); the author of one trial (8) informed us that he was unable to provide any additional information.

Description of Included Studies

Trials enrolled a median of 158.5 patients (range, 18–1508) and were conducted in one (6, 8, 10–14, 16) or two (7, 9) centers (Tables 1 and 2), except for two recently published, large, multicenter trials (15, 17; additional details in [18–21]). Enrolled patients had a critical illness (ie. trauma [6], pancreatitis [12], or various [7]), or were admitted to an ICU (8–11, 13–17) with AKI, defined by abnormal biochemistry (serum creatinine or urea) or a complication of oliguria (e.g., hyperkalemia or volume overload). Two trials required oliguria (9, 10). Seven trials specifically excluded patients with chronic renal failure (8, 9, 13, 16, 17) or end-stage renal disease

(14, 15). Patients had high illness severity (median Acute Physiology and Chronic Health Evaluation II score, 26 in 7 trials) and many had sepsis (median, 43.5% of enrolled patients in 12 trials).

Eleven trials used one modality exclusively: IHD (6–8), CRRT [CVVH (9, 10, 12); CVVH or CVVHD (11); CVVH or CVVHDF (13); CVVHDF (14, 15)], or SLED (16). Two of these trials used more than one CRRT mode and allocated patients to high-dose or standard-dose CVVH or CVVHD in a factorial design (11), or to high-dose CVVHDF vs. standard-dose CVVH (13). One trial studied high-dose vs. standard-dose RRT and assigned patients to IHD vs. CVVHDF or SLED based on hemodynamic stability (17). Trials of CVVH or CVVHDF administered replacement fluid either prefilter (12–14, 17) or postfilter (9–11, 15).

Two early trials of IHD (6, 7) targeted differential predialysis serum creatinine and urea in the high-dose and standard-dose groups, whereas other trials explicitly varied the frequency of IHD sessions (8, 17). Trials of IHD reported delivering 5.4 to 7.0 and 2.5 to 3.2 sessions per week in the high-dose and standard-dose arms, respectively (6–8, 17). Prescribed Kt/V_{urea} (a dimensionless coefficient defining urea clearance per session, where K is the dialyzer clearance of urea, t is time, and V_{urea} is the volume of distribution of urea), when reported, was 1.2 to 1.4 per session (8, 17), although the targeted Kt/V_{urea} was not achieved in one trial (8). One trial of SLED defined dose by target urea (<15 mmol/L vs. 20–25 mmol/L), with patients administered the high dose receiving approxi-

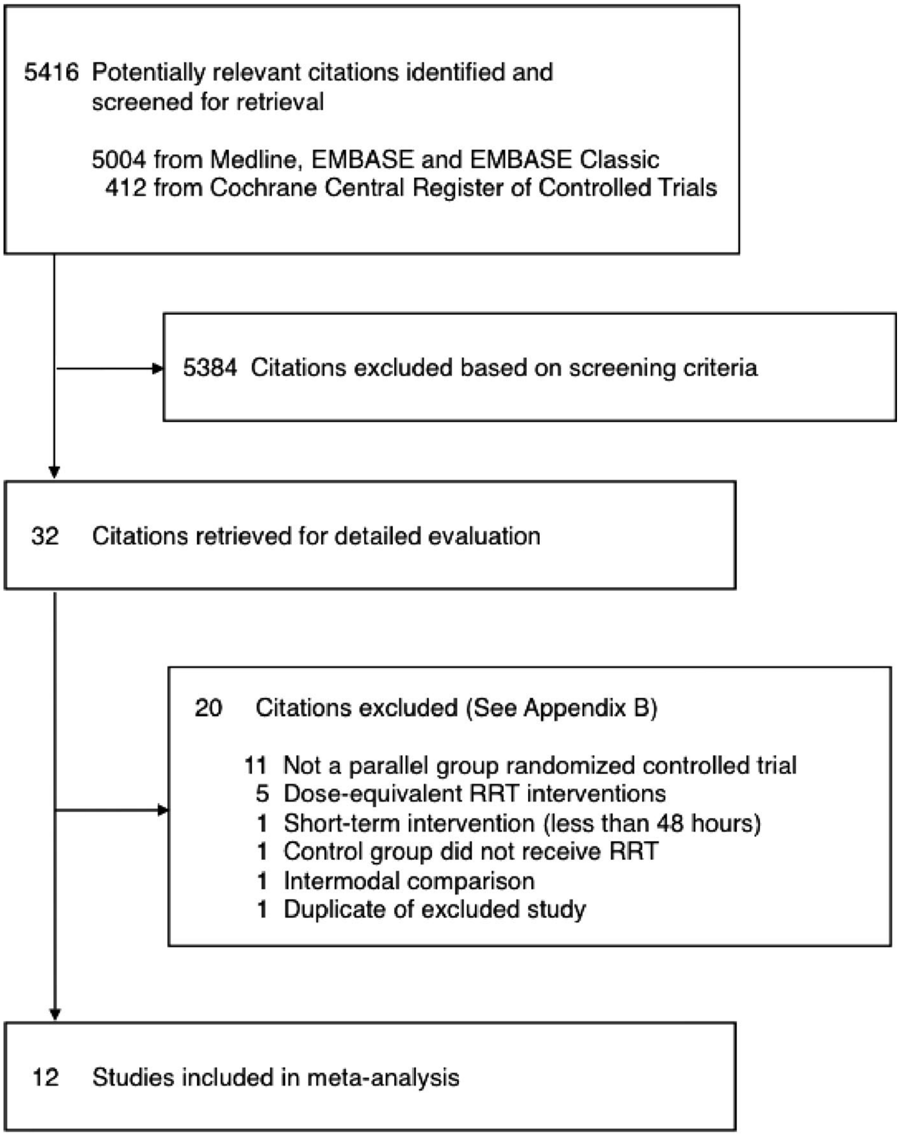

Figure 1. Flow of studies through the meta-analysis. *RRT*, renal replacement therapy.

Table 1. Patient characteristics in the included studies

Study	Patients Randomized, n	Centers, n	Age, yr	Male, %	APACHE II(/III)	Oliguria, %	Intensive Care Unit Days at Enrollment	Creatinine, μmol/L	Urea, mmol/L	Sepsis, %
Conger (6)	18	1	23	100	NR	94	NR	NR	NR	0[a]
Gillum et al (7)	34	2	56	85	NR	71	6[b]	NR	NR	38
Schiffl et al (8)	160	1	60	55	NR/87	46	NR	420	32	36
Bouman et al (9)	106	2	68	59	23/84	100	1.3	NR[c]	23	26
Ronco et al (10)	425	1	61	56	23	100	2.5	318	18	12
Morgera et al (11)	24	1	65	58	31	NR	NR	254	44	100
Jiang et al (12)	37	1	54	57	NR	84	NR[d]	232	12	32
Saudan et al (13)	206	1	63	61	25	37	3.9	428	30	60
Tolwani et al (14)	200	1	60	58	26	64	8	376	27	54
Bellomo et al (15)	1508	35	65	65	NR/102	60	2.1	334	23	49
Faulhaber-Walter et al (16)	157	1	51	63	32	73	5.9	273	22	72[e]
Palevsky et al (17)	1124	27	60	71	26	78	6.6[f]	362	24	63

APACHE, Acute Physiology and Chronic Health Evaluation [APACHE II (38); APACHE III (39)]; NR, not reported.

Continuous data are reported as means.

[a]Patients with septic shock causing acute kidney injury were excluded from the study, but the number of patients with sepsis (if any) was not reported; [b]there were 6 (SD, 3) days between acute kidney injury and initiation of intermittent hemodialysis – 5 (SD, 2) days in the high-dose group and 7 (SD, 3) days in the standard-dose group; [c]mean creatinine clearance 6 mL/min from 3-hr urine collection; [d]One-third of the patients were in the intensive care unit; [e]includes patients with the systemic inflammatory response syndrome; [f]interval from onset of acute kidney injury to randomization was 3.2 (SD, 2.0) days (37).

Table 2. Renal replacement interventions in the included studies

Study	Cessation of Study RRT[a]	High-Dose: Prescribed Dose[b]	High-Dose: Delivered Dose[b]; Days of Study RRT	High-Dose: Biochemistry During Therapy	Standard-Dose: Prescribed Dose[b]	Standard-Dose: Delivered Dose[b]; Days of Study RRT	Standard-Dose: Biochemistry During Therapy
Intermittent hemodialysis							
Conger (6)	Clinician	Cr <442; Urea <25	7.0/wk; 13.8 days	Cr = 309; Urea = 18 (pre-IHD)	Cr <884; Urea <54	2.5/wk; 12.2 days	Cr = 857; Urea = 43 (pre-IHD)
Gillum et al (7)	Clinician	Cr <442; Urea <21	6.1/wk; 18.3 days	Cr = 469; Urea = 21 (pre-IHD)	Cr <796; Urea <36	3.1/wk; 18 days	Cr = 804; Urea = 36 (pre-IHD)
Schiffl et al (8)	Clinician	Daily; Kt/V ≥1.2/ session	6.2/wk, Kt/V = 0.92/ session; 9 days	Cr = 468; Urea = 21 (time-averaged)	Alternate day; Kt/V ≥1.2/ session	3.2/wk, Kt/V = 0.94/ session; 16 days	Cr = 840; Urea = 37 (time-averaged)
Continuous renal replacement therapy							
Bouman et al (9) (postfilter CVVH)[c]	Protocol	≥72 L/day	48.2 mL/kg/hr; 2.9 days	NR	24–36 L/day	20.1, 19.0 mL/ kg/hr; 3.4 days	NR
Ronco et al (10) (postfilter CVVH)[d]	Clinician	35, 45 mL/kg/hr	33.6, 42.4 mL/ kg/hr; 13 days, 12 days	NR	20 mL/kg/hr	18.9 mL/kg/hr; 11 days	NR
Morgera et al (11) (postfilter CVVH and CVVHD)[e]	3 days	2.5 L/h (36 mL/ kg/hr)	NR; 2.8 days	NR	1 L/h (14 mL/kg/ hr)	NR; 2.8 days	NR
Jiang et al (12)(prefilter CVVH)[f]	Clinician	4 L/h (62 mL/kg/ hr)	NR; NR (≥3 days)	NR	1 L/h (16 mL/kg/ hr)	NR; NR (≥3 days)	NR
Saudan et al (13)(prefilter CVVH and CVVHDF)[g]	Protocol	42 mL/kg/hr	35 mL/kg/hr in 1st 24hr; NR	NR	25 mL/kg/hr	22 mL/kg/hr in 1st 24hr; NR	NR
Tolwani et al (14) (prefilter CVVHDF)	Clinician	35 mL/kg/hr	29 mL/kg/h; 10 days	NR	20 mL/kg/hr	17 mL/kg/hr; 9.7 days	NR
Bellomo et al (15) (postfilter CVVHDF)	Protocol	40 mL/kg/hr	33.4 mL/kg/hr; 6.3 days	Cr = 170; Urea = 13	25 mL/kg/hr	22 mL/kg/hr; 5.9 days	Cr = 204; Urea = 16
Sustained low-efficiency dialysis							
Faulhaber Walter et al (16)	Protocol	2 sessions in first 24 hrs, then target urea	13.3 sessions of 8.9 hrs each; NR	Urea = 14.7 (interdialytic interval)	1 session in first 24 hrs, then target urea <15 20–25	7.7 sessions of 8.5 hrs each; NR	Urea = 20.1 (interdialytic interval)
Combined modalities							
Palevsky et al (17) (prefilter CVVHDF, SLED, and IHD)[h]	Protocol	35 mL/kg/hr (CVVHDF); 6/wk, Kt/V 1.2–1.4/session (IHD)	35.8 mL/kg/hr; 7.8 days (CVVHDF); 5.4/wk, Kt/V 1.3/session; 13.4 days (IHD)	Urea = 12 (CVVHDF); Urea = 16 (before IHD), 12 (IHD, time-averaged)[i]	20 mL/kg/hr (CVVHDF); 3/wk, Kt/V 1.2-1.4/session (IHD)	22.0 mL/kg/hr; 7.3 days (CVVHDF); 3.0/wk, Kt/V 1.3/session; 12.8 days (IHD)	Urea =17 (CVVHDF); Urea = 25 (pre-IHD), 17 (IHD, time-averaged)[i]

Cr, creatinine (reported in μmol/L); CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration; IHD, intermittent hemodialysis; Kt/V, a dimensionless coefficient defining urea clearance per session, where K is the dialyzer clearance of urea, t is time and V is the volume of distribution of urea; NR, not reported; SLED, sustained low-efficiency dialysis.

Continuous data are expressed as means; urea is reported in mmol/L.

[a]Cessation refers to discontinuation of study renal replacement therapy by clinician discretion, by protocol (typically defining renal recovery), or when a fixed timepoint was reached; [b]prescribed and delivered doses refer to target urea or creatinine; number of weekly sessions or Kt/V per session (IHD, excluding the first session in one trial (17)); or effluent flow (continuous renal replacement therapy). For trials of continuous renal replacement therapy, effluent flow rates are as reported in the publications (expressed in weight-based units, if possible), without adjustment for the effects of net fluid removal or prefilter replacement fluid (if CVVH or CVVHDF used) on dose; [c]patients were randomized to 1 of 3 groups: high-dose or standard-dose CVVH starting ≤12 hrs after meeting inclusion criteria, or standard-dose CVVH starting only for clinical indications. In the last group, 6/36 (17%) patients did not receive RRT because of death (n=2) or renal recovery (n=4); [d]patients were randomized to 1 of 3 CVVH dose groups, 2 high-dose groups and 1 low-dose group; [e]patients were randomized to 1 of 4 groups: high-dose or standard-dose CVVH, or high-dose or standard-dose CVVHD. Weight-based prescribed doses are calculated based on an assumed mean weight of 70 kg; [f]patients were randomized to 1 of 4 groups: high-dose or standard-dose CVVH starting within 48 hrs or 96 hrs after the onset of abdominal pain. All patients had pancreatitis and acute kidney injury. Mean patient weight in each group was obtained from the author; [g]patients were randomized to a high-dose CVVHDF group (mean replacement 24 mL/kg/hr plus mean dialysate 18 mL/kg/hr) or a standard-dose CVVH group (mean 25 mL/kg/hr); [h]within the high-dose and standard-dose groups, patients received IHD if hemodynamically stable and CRRT or sustained low-efficiency dialysis (by centre preference) if unstable. Delivered doses for sustained low-efficiency dialysis sessions are not shown as this modality was uncommonly used; [i]time-averaged urea values taken from (37).

mately twice the number of sessions as patients receiving standard-dose RRT (16). Finally, four trials using CRRT prescribed dose in weight-based units (10, 14, 15, 17). Of the four other trials prescribing dose per unit time, completely (9, 11, 12) or partially (13) independent of weight, two reported the actual delivered dose in weight-based units (9, 13), one provided the mean patient weight per group (12), and for one trial we assumed a mean weight of 70 kg (11). For CRRT, high-dose effluent flow was 35–62 mL/kg/hr and standard-dose effluent flow was 14–25 mL/kg/hr, based on prescribed dose (9–15, 17).

The median duration of study RRT was 10 days (range, 2.8–18.3) in the high-dose group and 11 days (range, 2.8–18.0) in the standard-dose group. Trials discontinued study RRT after a fixed duration (11), at the

Table 3. Factors related to risk of bias of included trials

Study	Sequence Generation	Concealment of Allocation	Trial Stopped Early for Benefit	Intention-to-Treat Analysis	Postrandomization Withdrawals From Mortality Analysis
Conger (6)	Quasi-randomized[a] (alternate allocation within each subgroup)	No	Not reported[b]	Yes	No
Gillum et al (7)	Coin-flip to assign patients paired by etiology of acute kidney injury	Incomplete (second patient within pair not concealed)	Not reported[b]	Yes	No
Schiffl et al (8)	Quasi-randomized (alternate allocation)	No	No	Yes	No
Bouman et al (9)	Computer-generated	Yes (sequentially numbered sealed opaque envelopes)	No	Yes	No
Ronco et al (10)	Computer-generated	Yes (central randomization)	No	Yes	No
Morgera et al (11)	Not reported	Unclear (not reported)[c]	No[b]	Yes	No
Jiang et al (12)	Quasi-randomized (alternate allocation)	No	No	Yes	No
Saudan et al (13)	Computer-generated	Yes (sequentially numbered sealed opaque envelopes)	Yes[d]	Yes	No
Tolwani et al (14)	Computer-generated	Yes (sealed numbered envelopes)	No	Yes	No
Bellomo et al (15)	Computer-generated	Yes (central randomization)	No	Yes	High-dose: 26 of 747; standard-dose: 18 of 761 (includes refusal of delayed consent, withdrawal of consent, and loss to follow-up; not analyzed)
Faulhaber-Walter et al (16)	Computer-generated	Yes (local independent randomization by statistician)	No	Yes	High-dose: 0 of 81; standard-dose: 1 of 76 (did not meet inclusion criteria; not analyzed)
Palevsky et al (17)	Computer-generated	Yes (central randomization)	No	Yes	High-dose: 2 of 563; standard-dose: 3 of 561 (lost to follow-up and analyzed alive)

[a]If no patient with similar injuries had been previously treated, then the new patient was assigned by alternate allocation. If a patient's injury pattern was similar to another patient in the protocol, then the new patient was assigned the alternate treatment. Two patients were assigned by direct investigator allocation to the standard-dose arm "because they had injuries similar to other patients in [the high-dose arm] to which they could be compared;" [b]these trials did not report a sample size calculation; [c]we were unable to reach the author of this trial; [d]confirmed in correspondence with study author.

clinicians' discretion (6–8, 10, 12, 14), or when certain clinical criteria defined in the study protocol were met (9, 13, 15–17).

Study Quality

Most trials were at low risk for bias (9, 10, 14–17). All patients were analyzed according to the group (Table 3) to which they were initially assigned, and withdrawals of randomized patients from the mortality analysis either did not occur (6–14) or comprised <5% of randomized patients (15–17). Caregiver blinding was not practical in any trial. Seven trials (9, 10, 13–17) clearly concealed allocation, whereas three quasi-randomized trials used alternate allocation (6, 8, 12), one trial used a coin-flip to assign patients paired by etiology of AKI (7), and one trial did not report the method of allocation (11). The author of one trial informed us that it was stopped early for benefit (15).

Clinical Outcomes

Trials varied in the timing of mortality reporting: 6 mos (6), 90 days (13, 15), 60 days (17), or 28 days (16) after randomization; at discharge from the hospital (7, 9, 12, 14) or ICU (11); or 14 days (8) or 15 days (10) after cessation of RRT (which was provided for a mean of 9–16 days). Pooled mortality from 12 trials (n = 3954) showed no benefit of high-dose vs. standard-dose RRT (RR, 0.89; 95% CI, 0.77–1.03; $p = .12$) (Fig. 2). There was moderate statistical heterogeneity ($I^2 = 67\%$) in this analysis. Visual inspection of a funnel plot did not suggest publication bias (Appendix C).

Similarly, trials varied in the timing of reporting of dialysis dependence in survivors: 6 months (6), 90 days (13, 15), 71 days (9), 60 days (17), or 28 days (16) after randomization; at discharge from the hospital (7, 12, 14); or 14 days after cessation of RRT (8). Two trials (n = 68) reported no survivors requiring dialysis at last follow-up (6, 9). Data from eight trials (n = 1743) with events showed no effect of high-dose vs. standard-dose RRT on the risk of dialysis dependence in survivors (RR, 1.15; 95% CI, 0.92–1.44; $p = .23$) (Fig. 3). There was no evidence of statistical heterogeneity in this analysis ($I^2 = 0\%$).

Hypotension

Several trials reported hypotension during RRT, but widely variable definitions precluded meta-analysis. One multicenter trial (17) reported more patients in the high-dose vs. standard-dose group with hypotension requiring vasopressor therapy 81 of 563 [14.4%] vs. 56 of 561 [10.0%]; $p = .02$) or other intervention (212 of 563 [37.7%] vs. 168 of 561 [29.9%]; $p = .006$), but no difference in patients with hypotension requiring cessation of RRT (55 of 563 [9.8%] vs. 49 of 561 [8.7%]; $p = .55$).

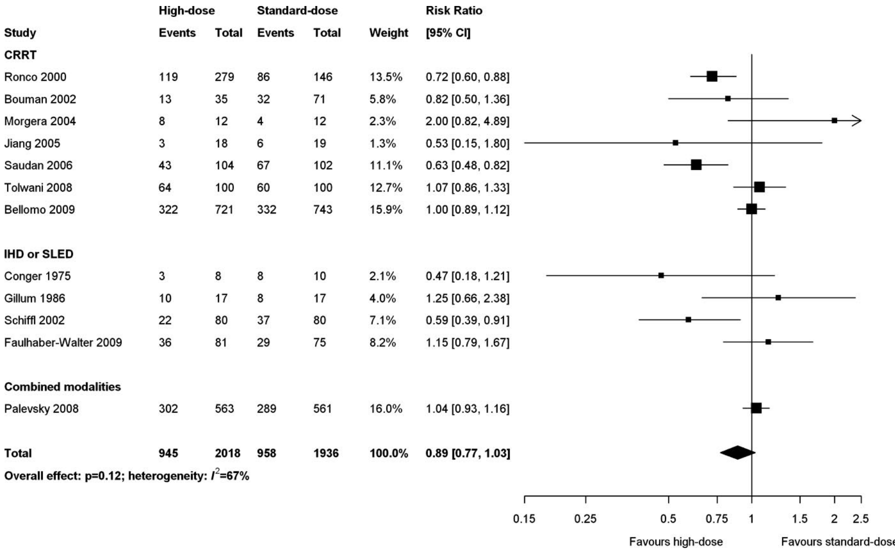

Figure 2. Effect of high-dose vs. standard-dose renal replacement therapy on mortality. The pooled risk ratio with 95% confidence interval (*CI*) was calculated using a random-effects model. Weight refers to the contribution of each study to the overall estimate of treatment effect. *CRRT*, continuous renal replacement therapy; *SLED*, sustained low-efficiency dialysis; *IHD*, intermittent hemodialysis.

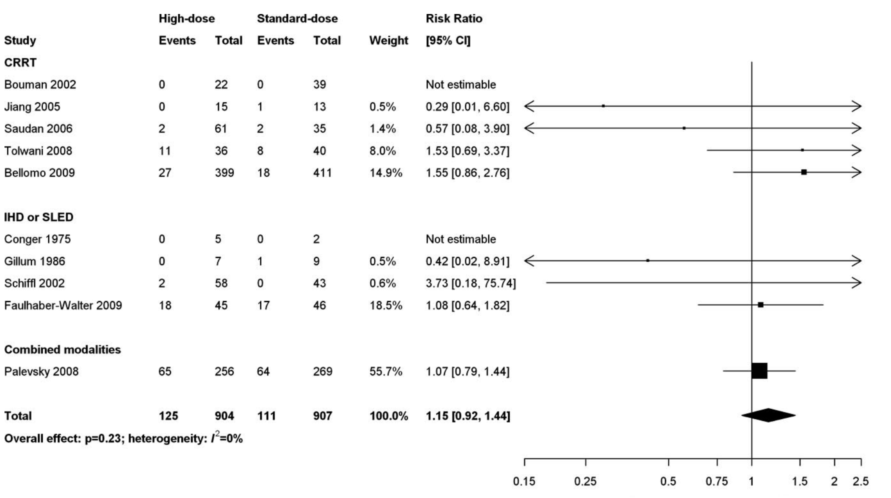

Figure 3. Effect of high-dose vs. standard-dose renal replacement therapy on dialysis dependence among survivors. The pooled risk ratio with 95% confidence interval (*CI*) was calculated using a random-effects model. Weight refers to the contribution of each study to the overall estimate of treatment effect. *CRRT*, continuous renal replacement therapy; *SLED*, sustained low-efficiency dialysis; *IHD*, intermittent hemodialysis.

We obtained supplemental information on hypotension from authors of three trials (10, 12, 16). One small trial reported a similar risk of hypotension (high-dose, 2 of 18 [11.1%] vs. standard-dose, 4 of 19 [21.2%]; $p = .66$ by Fisher's exact test) (12). In the trial of SLED (16), the number of days on which mean arterial pressure declined to <70 mm Hg or vasopressor support was required was similar (high-dose 7.8 ± 7.5 days vs. standard-dose 6.8 ± 7.0 days; $p = .39$). One trial reported "no difference" in hypotension episodes (10).

Sensitivity and Subgroup Analyses

When analyses were restricted to trials in which both groups started RRT at the same time after randomization, there was no effect of high-dose RRT on mortality (RR, 0.88; 95% CI, 0.76–1.03; 10 trials; n = 3866) (8–17) or dialysis dependence (RR, 1.15; 95% CI, 0.92–1.44; 7 trials with events; n = 1727) (8, 12–17). These analyses excluded two trials (6, 7) in which the high-dose and standard-dose groups started RRT at different times according to different biochemical targets, and one standard-dose group in one trial (9) in which RRT was started only for clinical indications (vs. the two other groups in which RRT was started within 12 hrs of meeting inclusion criteria).

The effect of high-dose vs. standard-dose RRT on mortality was similar in patients (Fig. 4): 1) with sepsis (RR, 1.02; 95% CI, 0.85–1.23; 9 trials; n = 1786) (9–17) and without sepsis (RR, 0.89; 95% CI, 0.75–1.05; 8 trials; n = 1955; interaction $p = .28$ for difference between RRs) (9, 10, 12–17); 2) treated exclusively with CRRT (RR, 0.87; 95% CI, 0.71–1.06; 7 trials; n = 2462) (9–15) vs. other modalities, exclusively or in a combined manner (RR, 0.92; 95% CI, 0.70–1.21; 5 trials; n = 1492; interaction $p = .75$) (6–8, 16, 17); and 3) enrolled in trials with low risk of bias (RR, 0.96, 95% CI, 0.85–1.09; 6 trials, n = 3475) (9, 10, 14–17) vs. trials at higher risk for bias because of no or unclear allocation concealment (6–8, 11, 12) or early stopping (13) (RR, 0.76; 95% CI, 0.53–1.09; 6 trials, n = 479; interaction $p = .23$). There was moderate heterogeneity ($I^2 = 50\%$ to 74%) in each of the subgroup and sensitivity analyses for mortality.

The effect of high-dose RRT on dialysis dependence in survivors was similar in patients treated exclusively with CRRT (RR, 1.41; 95% CI, 0.90–2.21; 4 trials with events; n = 1010) (12–15) vs. other modalities (RR, 1.07; 95% CI, 0.83–1.39; 4 trials with events; n = 733; interaction $p = 0.30$) (7, 8, 16, 17). There was no evidence of heterogeneity ($I^2 = 0\%$) in either analysis.

DISCUSSION

The main results of this systematic review and meta-analysis are that high-dose RRT for patients with AKI does not reduce mortality or dialysis dependence in survivors. Our results are consistent with a large observational study (22) and with two recent, multicentered, randomized trials included in the meta-analysis (15, 17), strengthening our conclusions. Our novel finding is that results were consistent among subgroups defined by presence of sepsis and modality of RRT (continuous vs. intermittent).

Strengths of our review include methods to minimize bias: a comprehensive literature search, duplicate data abstraction, consideration of important clinical outcomes, and inclusion of additional methodologic or clinical information from two-thirds of included trials. Most included

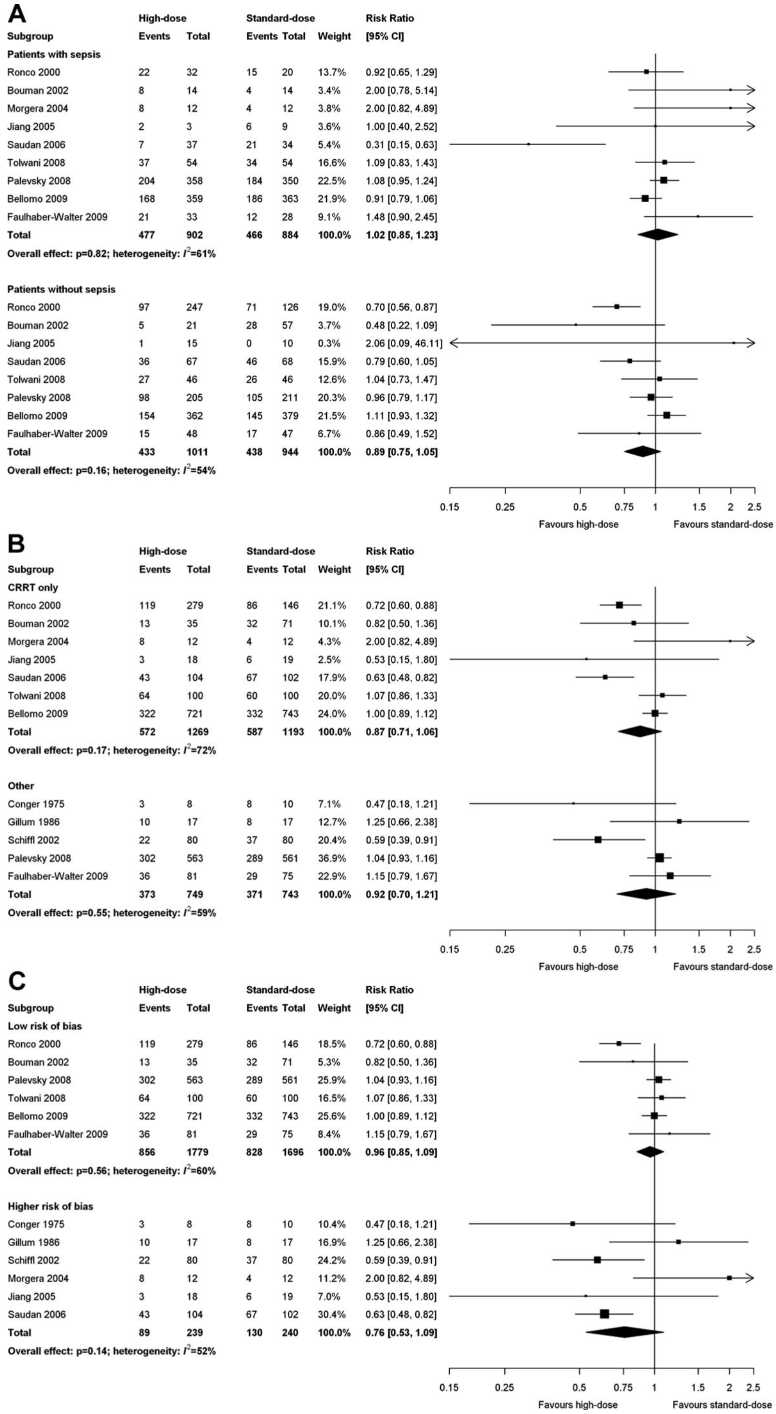

Figure 4. Effect of high-dose vs. standard-dose renal replacement therapy on mortality. Subgroup analyses are shown for (*A*) patients with and without sepsis (interaction $p = .28$ for difference between risk ratios), (*B*) patients treated exclusively with continuous renal replacement therapy (*CRRT*) vs. other individual or combinations of modalities (interaction $p = .75$), and (*C*) studies with low risk for bias vs. higher risk for bias (interaction $p = .23$). Pooled risk ratios were calculated using random-effects models. Weight refers to the contribution of each study to each subgroup's estimate of treatment effect. In the Saudan 2006 study (13), the sepsis group in (*A*) includes patients specifically with sepsis-induced acute kidney injury. In (*B*), all patients in the Palevsky 2008 study (17) are included in the "other" subgroup. Alternatively, if the patients who received CRRT/sustained low-efficiency dialysis as initial modality in this trial are included in the "CRRT only" subgroup, then results are similar, i.e., CRRT only vs. other therapies: risk ratio, 0.89; 95% confidence interval (*CI*), 0.76–1.04 vs. risk ratio, 0.93; 95% CI, 0.68–1.29; interaction $p = .81$. Note that the CRRT group for this trial includes patients who received sustained low-efficiency dialysis, although the number of sustained low-efficiency dialysis treatments was small (≈5% of the number of CRRT sessions) (17).

trials were at low risk for bias. Although the 12 included trials assessed mortality at variable times, 10 of them evaluated mortality ≥28 days after randomization or at ICU or hospital discharge. An important limitation in the mortality analyses is the moderate statistical heterogeneity, suggesting that high-dose RRT may benefit a subgroup defined by patient characteristics or RRT procedure. However, there was no benefit in two prespecified and important clinical subgroups of septic patients and patients treated exclusively with CRRT.

Trials included in this review varied in RRT modality, dose, and timing of initiation, reflecting the diversity of clinical practice informing trial methodology. The dose arms within each trial shared the same modality, except for one trial that applied different modalities based on hemodynamic considerations unrelated to RRT dose (17). To investigate modality as a modifier of the effect of high-dose RRT, we performed a subgroup analysis of trials applying continuous vs. intermittent therapies and found no difference in effect. We considered performing a subgroup analysis to assess whether high-dose RRT benefits patients when started early, but variable definitions of AKI precluded a reliable assessment of timing of RRT initiation. Other recent meta-analyses have not found differential outcomes based on RRT modality or timing of initiation (3, 23, 24). Trials also varied in the RRT doses being compared. We categorized arms within trials as high-dose and low-dose based on consensus among the investigators. More fundamentally, the concept of RRT dose as defined by urea clearance does not incorporate other considerations, such as clearance of inflammatory mediators or achievement of desired fluid balance. It also presents operational challenges because there is no commonly accepted method of expressing dose across RRT modalities. For example, the Kt/V_{urea} measure used for IHD is based on steady-state assumptions for chronic hemodialysis and may underestimate actual urea clearance for intermittent therapies in patients with AKI (25). Despite these limitations, urea clearance remains widely used to measure RRT dose.

The results of our review support current clinical practice (26–28). In the United States, a survey (26) of 27 ICUs enrolling patients in a clinical trial (17) reported that most clinicians (>80%) prescribed a standard fixed dose of CRRT (median, 1825 mL/hr; interquartile range, 1200–2400 mL/hr; or 22 mL/kg/hr; 14–29 mL/kg/hr, assuming a mean patient weight of 84 kg [17]) and three to four sessions of IHD per week. Another survey of 34 ICUs in Australia and New Zealand (27) enrolling patients in a trial (15) estimated the mean prescribed CRRT dose as 24 mL/kg/hr; all sites prescribed dose independent of weight. Finally, a multicenter cohort study (54 ICUs in 23 countries) of CRRT practice (28) reported that only 12% of patients received doses exceeding 35 mL/kg/hr.

High-dose therapy is of theoretical interest for patients with sepsis-induced AKI, in whom proinflammatory mediators are increased (29). We detected no effect of high-dose RRT in patients with AKI and sepsis. However, our review does not address the role of RRT in patients with sepsis who have not yet developed AKI. Several trials have studied hemofiltration in patients with early sepsis or the systemic inflammatory response syndrome, but the effects are inconsistent (30–33). Another unanswered question is whether very-high-dose RRT improves outcomes compared to high-dose RRT. A 20-patient, randomized, controlled trial found that norepinephrine requirements were reduced in patients receiving CVVH at 65 mL/kg/hr compared to 35 mL/kg/hr (34). The ongoing IVOIRE (high VOlume in Intensive Care) randomized, controlled trial (Clinicaltrials.gov NCT00241228; planned n = 460) is comparing very-high vs. high-dose strategies in septic shock and AKI and should provide additional information.

Although we have not shown a benefit of high-dose RRT, clinicians should be wary of underdosing RRT in AKI. We believe that patients with AKI prescribed CRRT should receive a minimum effluent volume of 20 mL/kg/hr, and clinicians should consider temporarily increasing the dose to compensate for times during which therapy is held. For patients receiving intermittent modalities, alternate day therapy may be acceptable as long as a Kt/V_{urea} exceeding 1.2 is attained in each session.

CONCLUSION

Current evidence does not demonstrate reduced mortality or dialysis dependence in patients with AKI who receive high-dose RRT. This finding is consistent across modalities of RRT and in patients with sepsis.

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APPENDIX A

Search Strategy

We searched the following databases: Ovid MEDLINE 1950 to October 2009, week 5; EMBASE Classic and EMBASE 1947 to week 44, 2009; and EBM Reviews – Cochrane Central Register of Controlled Trials Third Quarter 2009.

1. (CRRT or CVV$ or CAVH or CAVHD or CAVHDF or IHD or SCUF).mp.
2. (contin$ adj4 (dialy$ or diafilt$ or hemodia$ or hemodia$ or hemofilt$ or hemofilt$ or filt$ or ultrafilt$ or arterioven$ or venoven$)).mp.
3. (intermittent adj4 (dialy$ or diafilt$ or hemodia$ or hemodia$ or hemofilt$ or hemofilt$ or filt$ or ultrafilt$ or arterioven$ or venoven$)).mp.
4. ((non-continu$ or noncontinu$ or discontinu$) adj4 (dialy$ or diafilt$ or hemodia$ or hemodia$ or hemofilt$ or hemofilt$ or filt$ or ultrafilt$ or arterioven$ or venoven$)).mp.
5. (SLED or SLEDD or SLEDDF or SLEDD-F). mp.
6. ((sustained or slow) adj4 (low efficiency or low-efficiency) adj4 (daily dialy$ or daily diafilt$ or dialy$ or diafilt$ or hemodia$ or hemodia$ or hemofilt$ or hemofilt$)).mp.
7. renal replacement therapy/or renal dialysis/or hemodiafiltration/or hemofiltration/or hemodialysis/or exp continuous renal replacement therapy/or extended daily dialysis/
8. or/1–7 [RRT terms]
9. exp sepsis/or exp systemic inflammatory response syndrome/or exp septic shock/or exp Shock, Septic/or exp Multiple Organ Failure/
10. exp Critical Illness/or exp critical care/or exp intensive care/or exp Intensive Care Units/or exp intensive care unit/
11. (sepsis or SIRS).mp.
12. or/9–11 [sepsis and ICU terms]

13. Exp Kidney Failure, Acute/
14. (acute renal failure or acute renal injury or acute renal insufficiency or acute kidney injury or acute kidney failure or acute kidney insufficiency).mp.
15. 13 or 14 [AKI terms]
16. clinical trial.mp. or clinical trial.pt. or random:.mp. or tu.xs. [MEDLINE sensitive filter for randomized trials]
17. random:.tw. or clinical trial:.mp. [EMBASE sensitive filter for randomized trials]
18. 8 and 12 and (16 or 17)
19. 8 and 15 and (16 or 17)
20. remove duplicates from 18
21. remove duplicates from 19
22. 20 or 21
23. remove duplicates from 22

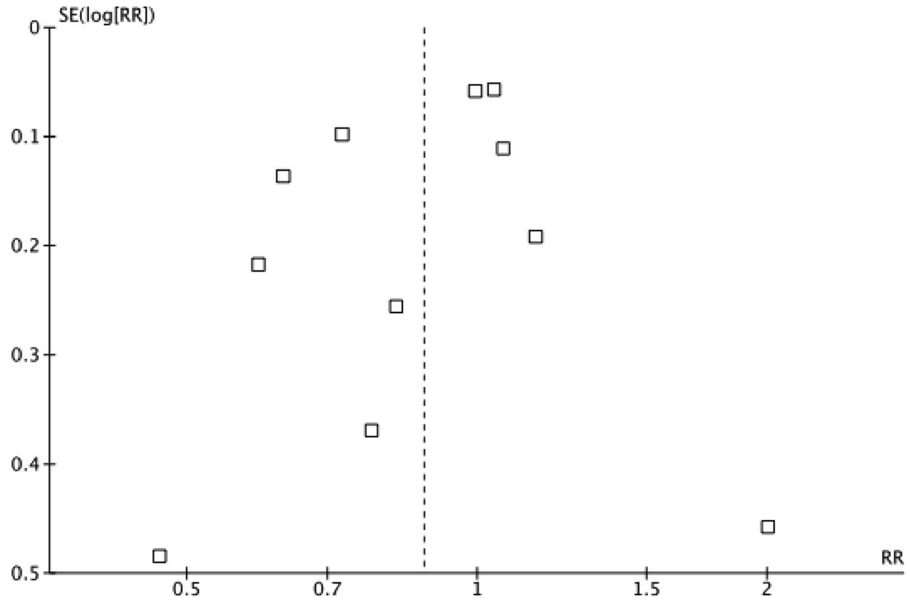
Notes: '$' retrieves unlimited suffix variations; the .mp. extension includes the title, original title, abstract, and subject heading fields in all databases; .tw. refers to textword. Filters for MEDLINE and EMBASE (lines 2 and 5) are based on published sensitive strategies for retrieving randomized trials (40, 41). We also used British spelling of all textwords whenever relevant (i.e. "haemodia$" in item 2).

APPENDIX C

Funnel plot for pooled analysis of mortality.

Each point represents one trial.

RR, risk ratio; *SE*, standard error.



Appendix B. Reasons for exclusion of retrieved studies

Study	Year	Main Reason For Exclusion
Bellomo (42)	1994	Not a parallel group, randomized, controlled trial
Booth et al (43)	1995	
Brause et al (44)	2003	
Hirasawa et al (45)	1991	
Hirayama et al (46)	2003	
Hubsher et al (47)	1986	
Lins et al (48)	2005	
Maher et al (49)	1988	
Storck et al (50)[a]	1991	
Raja et al (51)	1986	
Zhang[a] et al (52)	2004	
Daud et al (53)	2006	Dose-equivalent renal replacement therapy interventions
Favre et al (54)	1996	
Koo et al (55)	2006	
Pettila et al (56)	2001	
Pursnani[b] et al (36)	1997	
Alamartine[c] et al (35)	1994	Short-term intervention (<48 hrs) and no outcome data available
Davenport et al (57)	1993	Intermodal comparison
Riegel et al (58)	1995	Control group did not receive renal replacement therapy
Inthorn et al (59)	1991	Duplicate of Storck 1991 (50)

[a]This trial was incompletely randomized because some patients were directly assigned to one group depending on device availability; [b]author provided additional information; [c]author confirmed that no additional clinical outcomes data were available.