



Effectiveness of Renal Replacement Therapy in Severe Acute Kidney Injury: A Systematic Review of Randomized Controlled Trials

¹ Muhamad Luthfi Asyhar, ² Rifqi Alridjal, ³ Muhammad Thoriq Alhabib, ⁴ Muhammad Fajar Ramadhan, ⁵ M. Josie Yusuf, ⁶ Ellya Catharine, ⁷ Saga Ahan Sahaya, ⁸ Charles Sanjaya

¹ General Practitioner, Waras Wiris Regional General Hospital, Indonesia /
Graduate of Faculty of Medicine, Airlangga University, Indonesia

² General Practitioner, Jakarta Islamic General Hospital, Pondok Kopi, Indonesia /
Graduate of Faculty of Medicine, Veteran National Development University,
Indonesia

³ General Practitioner, Karya Medika 1 General Hospital, East Bekasi, Indonesia /
Graduate of Faculty of Medicine, University of Andalas, Indonesia

⁴ General Practitioner, Bunda Mulia General Hospital, Indonesia / Graduate of
Faculty of Medicine, University of YARSI, Indonesia

⁵ General Practitioner, Malang City General Hospital, Indonesia / Graduate of
Faculty of Medicine, Malang Islamic University, Indonesia

⁶ General Practitioner, Bakti Timah General Hospital, Pangkalpinang, Indonesia /
Graduate of Faculty of Medicine, University of Tanjungpura, Indonesia

⁷ General Practitioner, Graduate of Faculty of Medicine, Malang Islamic University,
Indonesia

⁸ Internist, Kebonjati General Hospital, Indonesia

Corresponding Email : muhamadluthfiasyhar@yahoo.com

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ABSTRACT

Introduction: Severe acute kidney injury (AKI) affects a substantial proportion of critically ill adults, with mortality approaching 50% once renal replacement therapy (RRT) becomes necessary. Four core prescriptive decisions—timing of initiation, intensity of clearance, modality selection, and anticoagulation strategy—remain contested. This systematic review aimed to determine whether any specific RRT strategy improves survival, kidney recovery, circuit performance, and safety in adults with severe AKI across all four domains.

Methods: The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines from inception to 30 April 2026 for randomized controlled trials (RCTs) enrolling adults with severe AKI (KDIGO stage 2–3 or equivalent) comparing RRT strategies. Two reviewers independently screened records, extracted data, and appraised risk of bias using Cochrane RoB 2; certainty was rated with GRADE. Fifteen outcome domains were pre-specified. Evidence was synthesised within domain using structured narrative synthesis with effect-direction tabulation.

Results: Twenty-nine RCTs enrolling 12,129 participants were included (9 timing trials, 8 dose/intensity trials, 7 modality trials, and 5 anticoagulation trials). Overall risk of bias was low in 8 trials, of some concern in 19, and high in 2. No RRT strategy reduced all-cause mortality: 90-day mortality was 43.9% versus 43.7% for accelerated versus standard initiation

(RR 1.00, 95% CI 0.93–1.09; $P=0.92$) and 44.7% in both arms of higher- versus lower-intensity continuous RRT (OR 1.00, 95% CI 0.81–1.23; $P=0.99$). Accelerated initiation significantly increased RRT dependence among 90-day survivors (10.4% vs 6.0%; RR 1.74, 95% CI 1.24–2.43) and adverse events (23.0% vs 16.5%; $P<0.001$); excessive postponement was significantly harmful (adjusted HR for 60-day death 1.65, 95% CI 1.09–2.50; $P=0.018$). A delayed strategy spared RRT entirely in 38–49% of patients. Regional citrate anticoagulation significantly prolonged filter life span (47 vs 26 h; difference 15 h, 95% CI 11–20; $P<0.001$) and halved bleeding complications (5.1% vs 16.9%; $P<0.001$). Higher-intensity clearance significantly increased hypophosphataemia (65% vs 54%; $P<0.001$) and prolonged mechanical ventilation (HR for extubation 0.67, 95% CI 0.52–0.88). Sustained low-efficiency dialysis significantly reduced ventilator days, ICU days, transfusion volume, and nursing cost versus continuous haemofiltration.

Discussion: The consistent null effect on mortality across 12,129 randomised patients, with an individual-patient-data meta-analysis showing no heterogeneity, indicates that survival in severe AKI is governed by underlying critical illness rather than extracorporeal prescription once a threshold of adequacy is reached. Therapeutic gains are therefore not in survival but in avoidance of unnecessary therapy, protection of kidney recovery, circuit longevity, bleeding avoidance, and resource preservation—outcomes on which the evidence is statistically significant, internally consistent, and directly actionable.

Conclusion: In adults with severe AKI, no timing, dose, or modality strategy improves survival. A watchful-waiting strategy with strictly defined mandatory triggers, a delivered continuous effluent dose of 20–25 mL/kg/h (or thrice-weekly intermittent haemodialysis with Kt/V 1.2–1.4), modality selection driven by haemodynamics and local resources, and regional citrate as the default anticoagulant constitute the evidence-based standard. Postponement must not, however, be indefinite.

Keywords: Acute kidney injury; renal replacement therapy; continuous renal replacement therapy; critical illness; regional citrate anticoagulation

INTRODUCTION

Background

Acute kidney injury (AKI) is the single most frequent organ dysfunction encountered in the intensive care unit (ICU). The multinational Acute Kidney Injury–Epidemiologic Prospective Investigation (AKI-EPI), which prospectively applied the complete Kidney Disease: Improving Global Outcomes (KDIGO) definition to 1,802 patients across 97 centres, demonstrated that 57.3% of ICU patients develop AKI during the first week of admission, and that the adjusted odds of hospital death rise stepwise with severity, reaching 6.88 (95% CI 3.88–12.23) for stage 3 disease. Survivors do not escape unscathed: almost half leave hospital with an estimated glomerular filtration rate below 60 mL/min/1.73 m², compared with 14.8% of patients who never developed AKI.¹

The burden is amplified in specific phenotypes. Sepsis-associated AKI occurs in approximately one in six ICU admissions and in nearly half of all septic patients, and is independently associated with mortality even after adjustment for illness severity. Surgery-associated AKI complicates roughly one in five major operations requiring postoperative critical care, and 8.7% of affected patients require renal replacement therapy (RRT) in the ICU. These two phenotypes together account for the overwhelming majority of patients who ultimately receive extracorporeal renal support.^{2,3}

Epidemiological data from resource-variable settings, which are of particular relevance to Indonesian and wider South-East Asian practice, show a comparable incidence of AKI but consistently worse outcomes, with higher dialysis requirements, longer ICU stay and higher case fatality than in high-income cohorts. In a nationwide Laotian ICU cohort, AKI occurred in 34.8% of admissions and mortality rose from 4.9% in stage 1 to 66.8% in stage 3, yet only 1.8% of the entire cohort ever received RRT—an eloquent illustration of the gap between need and delivery in the region.^{4,5}

Against this background, RRT remains the only supportive therapy capable of correcting the life-threatening consequences of severe AKI: refractory hyperkalaemia, decompensated metabolic

acidosis, diuretic-resistant pulmonary oedema and overt uraemic complications. Nationwide administrative data from Japan covering 51,758 ICU patients starting RRT between 2007 and 2016 confirm a genuine secular improvement in adjusted in-hospital mortality (adjusted odds ratio 0.66, 95% CI 0.60–0.72 in 2016 versus 2007), but crude mortality nonetheless remained above one third, underscoring how far short of satisfactory the current standard of care remains. ⁶

Crucially, when the classical emergency indications are absent, four prescriptive decisions must still be made at the bedside for every patient: (i) the timing of initiation, (ii) the intensity or delivered dose of clearance, (iii) the modality—continuous, intermittent or hybrid—and (iv) the anticoagulation strategy used to preserve the extracorporeal circuit. Each of these decisions has been the subject of randomized experimentation over the past twenty-five years, yet they have almost never been appraised together, and clinicians consequently continue to apply strategies whose evidentiary basis is heterogeneous and, in places, actively contradicted by the highest-quality trials. ⁷

Research Gap

Three specific gaps motivate the present review. First, existing evidence syntheses are domain-restricted: the large and methodologically rigorous syntheses of the last decade have addressed timing of initiation in isolation, leaving dose, modality and anticoagulation to separate and often older reviews, so that no single document supports the full sequence of decisions a clinician must actually make. Second, the timing literature itself is internally contradictory: early observational syntheses reported a 55% reduction in the odds of death with earlier RRT, whereas subsequent randomized syntheses and an individual-patient-data meta-analysis found precisely no effect, a discordance that has never been fully reconciled for the practising intensivist. Third, and most importantly, the field has continued to privilege all-cause mortality as the arbiter of effectiveness even though that endpoint has been definitively neutral across successive adequately powered trials, while outcomes that are demonstrably modifiable—unnecessary exposure to RRT, kidney recovery, catheter-related infection, circuit longevity, bleeding, and resource consumption—remain scattered, inconsistently reported and un-synthesized. ^{46,47,51}

Novelty

This review is, to our knowledge, the first to appraise all four RRT prescriptive domains—timing, dose, modality and anticoagulation—within a single PRISMA 2020-compliant randomized-evidence framework applying a uniform RoB 2 and GRADE appraisal, and the first to organize the synthesis around fifteen pre-specified outcome domains rather than mortality alone. Three further features are novel. First, we explicitly separate outcomes on which the randomized evidence is genuinely null from those on which it is statistically significant and clinically decisive, and we tabulate the latter as an actionable evidence set. Second, we integrate the pre-specified secondary and post hoc analyses of the landmark trials—including the AKIKI sepsis/ARDS analysis, the IDEAL-ICU diagnostic-criterion substudy, the AKIKI 2 coma analysis, the ATN mechanical-ventilation analysis and the RENAL four-year follow-up—so that the synthesis reflects the totality of randomized information rather than primary publications only. Third, we frame the final recommendations for resource-variable settings, in which the choice between continuous, hybrid and intermittent modalities and between citrate and heparin has direct and quantifiable cost implications.^{40,41,42,43,45}

Objectives

General objective: to determine, on the basis of randomized controlled trials, whether any specific renal replacement therapy strategy improves clinically important outcomes in adults with severe acute kidney injury.

Specific objectives:

- To quantify the effect of accelerated/early versus standard/delayed initiation of RRT on short-, medium- and long-term all-cause mortality.
- To quantify the effect of higher- versus lower-intensity RRT (effluent dose or dialysis frequency) on mortality and kidney recovery.
- To compare continuous, intermittent and hybrid (sustained low-efficiency dialysis) modalities with respect to survival, haemodynamic tolerance and organ-support burden.
- To compare regional citrate with systemic heparin anticoagulation with respect to filter life span, bleeding, infection and mortality.

- To determine the effect of each strategy on kidney recovery, long-term dialysis dependence and avoidance of RRT altogether.
- To characterize the safety profile of each strategy, including catheter-related bloodstream infection, metabolic derangement, haemodynamic instability and transfusion requirement.
- To appraise the methodological quality of the randomized evidence base and to grade the certainty of evidence for each outcome domain.

Hypotheses

H₀ (null hypothesis): In adults with severe AKI, neither accelerated initiation, higher-intensity clearance, continuous modality nor regional citrate anticoagulation confers a statistically significant reduction in all-cause mortality compared with the respective comparator strategies.

H₁ (alternative hypothesis): At least one of the strategies examined confers a statistically significant reduction in all-cause mortality.

H₂ (secondary directional hypothesis, pre-specified): Irrespective of the mortality result, strategies differ significantly with respect to non-fatal outcomes—specifically, that a delayed strategy significantly reduces exposure to RRT and catheter-related bloodstream infection, that accelerated initiation significantly increases dependence on RRT among survivors, that higher-intensity clearance significantly increases metabolic complications, and that regional citrate significantly prolongs filter life span and significantly reduces bleeding.

Benefits of the Study

- Theoretical benefit: consolidation of twenty-five years of randomized experimentation into a single appraised framework, clarifying which components of the RRT prescription are causally related to outcome and which are not, and thereby redirecting the research agenda towards kidney-recovery and phenotype-enriched designs.
- Clinical benefit: provision of an explicit, evidence-graded decision sequence covering initiation triggers, prescribed dose, modality selection and anticoagulation, directly usable at the ICU bedside and in institutional protocols.

- Health-system and economic benefit: quantification of the proportion of patients in whom RRT can be safely avoided altogether, and of the circuit-longevity and transfusion savings attributable to citrate anticoagulation and hybrid modalities—both of first-order importance in resource-variable settings such as Indonesia.
- Educational benefit: a structured, fully referenced resource for specialist and residency (PPDS) training in nephrology, anaesthesiology–intensive care and internal medicine.

METHODS

Protocol, registration and reporting standard

This systematic review was designed, conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement, including the 27-item main checklist and the 12-item abstract checklist. The review protocol was drafted a priori and specified the population, comparisons, outcome domains, search strategy, risk-of-bias instrument and synthesis plan before the formal search was executed. Any deviation from the protocol is reported explicitly in Section 2.11. Methodological conduct followed contemporary standards for critical appraisal of syntheses in nephrology.^{8,10}

Eligibility criteria (PICOS)

Element	Inclusion criteria	Exclusion criteria
Population (P)	Adults (≥ 18 years) who were critically ill or hospitalized with severe acute kidney injury, defined as KDIGO stage 2–3, RIFLE Injury/Failure, AKIN stage 2–3, or an explicit trial-specific equivalent (e.g. progressive azotaemia with an accepted clinical indication for dialysis).	Children and neonates; end-stage kidney disease already on maintenance dialysis; kidney transplant recipients as the sole population; AKI managed exclusively without any extracorporeal support in both arms.
Intervention (I)	Any renal replacement therapy strategy: accelerated/early initiation; higher-intensity (higher effluent dose or higher session	Pharmacological renoprotective agents; extracorporeal blood purification for indications other than AKI (e.g. isolated

Element	Inclusion criteria	Exclusion criteria
	frequency); continuous modality; hybrid modality; regional citrate anticoagulation.	cytokine adsorption without renal indication); peritoneal dialysis in adults (insufficient randomized data in the severe ICU population).
Comparator (C)	The corresponding alternative strategy: standard/delayed or more-delayed initiation; lower-intensity clearance; intermittent haemodialysis; systemic heparin anticoagulation.	Historical or non-concurrent controls.
Outcomes (O)	At least one of the 15 pre-specified outcome domains listed in Section 2.6.	Studies reporting only surrogate laboratory clearance without any clinical or safety outcome.
Study design (S)	Randomized controlled trials, including pilot and feasibility RCTs, published as full peer-reviewed papers in English.	Observational studies, quasi-randomized studies (alternate allocation), crossover studies of physiological endpoints only, conference abstracts, protocols without results, narrative reviews, editorials, case reports.

KDIGO = Kidney Disease: Improving Global Outcomes; RIFLE = Risk, Injury, Failure, Loss, End-stage kidney disease; AKIN = Acute Kidney Injury Network.

Search Strategy

The keywords used for this research based PICO :

PICO Element	Keyword 1	Keyword 2	Keyword 3
P (Population)	Adults with Severe	Critically Ill	ICU Patients

	Acute Kidney Injury	Patients with AKI	Requiring Renal Replacement Therapy
I (Intervention)	Renal Replacement Therapy Strategy	Timing of RRT Initiation	Regional Citrate Anticoagulation
C (Comparison)	Standard vs. Delayed Initiation of RRT	Higher- vs. Lower-Intensity Clearance	Continuous vs. Intermittent vs. Hybrid Modality
O (Outcome)	All-Cause Mortality	Kidney Recovery	Circuit Life Span and Bleeding Complications

The Boolean MeSH keywords inputted on databases for this research are: (*"Severe Acute Kidney Injury" OR "Critically Ill Patients" OR "ICU Patients"*) AND (*"Renal Replacement Therapy" OR "RRT Initiation Timing" OR "Regional Citrate Anticoagulation"*) AND (*"Standard Initiation" OR "Delayed Initiation" OR "Lower-Intensity Clearance" OR "Intermittent Hemodialysis" OR "Systemic Heparin"*) AND (*"All-Cause Mortality" OR "Kidney Recovery" OR "Circuit Life Span" OR "Bleeding Complications"*)

Study selection

All retrieved records were imported into reference-management software and de-duplicated. Two reviewers independently screened titles and abstracts against the eligibility criteria, then independently assessed the full text of all potentially eligible records. Disagreement at either stage was resolved by discussion and, where consensus was not reached, by adjudication from a third senior reviewer. Inter-reviewer agreement at the full-text stage was substantial (Cohen's $\kappa = 0.87$). The flow of records is presented in Table 2 in the format of the PRISMA 2020 flow diagram.⁸

Data extraction

Data were abstracted in duplicate onto a piloted standardized form capturing: bibliographic identifiers; country, number of participating centres and recruitment period; sample size randomized

and analysed; population definition and AKI criteria applied; baseline age, sex, illness-severity score and proportion with sepsis, mechanical ventilation and vasopressor support; the precise definition of the experimental and comparator strategies including numerical thresholds; the modality and delivered dose actually achieved; the anticoagulation protocol; all pre-specified outcomes with the corresponding effect estimates, confidence intervals and P values as reported by the trial authors; duration of follow-up; funding source; and trial registration number. Where a trial reported both intention-to-treat and per-protocol analyses, the intention-to-treat result was extracted as primary. Numerical values were extracted exactly as published; no imputation or back-calculation of unreported estimates was undertaken.

Pre-specified outcome domains

#	Outcome domain	Operational definition
O1	All-cause mortality at 28–30 days	Death from any cause within 28 or 30 days of randomization, as reported.
O2	All-cause mortality at 60 days	Death from any cause at day 60 (or the trial's equivalent medium-term timepoint).
O3	All-cause mortality at 90 days	Death from any cause at day 90; the contemporary standard primary endpoint in critical-care nephrology.
O4	ICU and in-hospital mortality	Death occurring before ICU discharge and before hospital discharge respectively.
O5	Recovery of kidney function	Independence from RRT with an acceptable clearance at the trial-defined timepoint, among survivors.
O6	RRT dependence in survivors	Continued requirement for any form of dialysis at day 28, 60, 90 or beyond, among those alive at that timepoint.
O7	Avoidance of RRT / RRT-free days	Proportion of patients allocated to a delayed strategy who never received RRT, and days alive and free of RRT to day 28.

#	Outcome domain	Operational definition
O8	Duration of RRT support	Number of days of extracorporeal renal support, or time to liberation from RRT.
O9	Extracorporeal circuit (filter) life span	Functional survival of the haemofilter or dialyser, in hours.
O10	Infectious complications	Catheter-related bloodstream infection and any new infection acquired after randomization.
O11	Bleeding and transfusion requirement	Any bleeding event attributable to the strategy, and red-cell transfusion volume or units.
O12	Metabolic and electrolyte complications	Hypophosphataemia, hypocalcaemia, hypokalaemia, metabolic alkalosis, citrate accumulation.
O13	Haemodynamic instability	Intradialytic hypotension, new or escalating vasopressor requirement, vasopressor-free time.
O14	Mechanical ventilation and organ-support burden	Ventilator days, ventilator-free days, time to successful extubation, SOFA-score trajectory.
O15	Length of stay and resource utilization	ICU and hospital length of stay, nursing time, and direct cost of therapy.

Risk-of-bias assessment

Risk of bias was assessed independently and in duplicate using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2), across its five domains: (D1) bias arising from the randomization process; (D2) bias due to deviations from intended interventions, evaluated for the effect of assignment to intervention; (D3) bias due to missing outcome data; (D4) bias in measurement of the outcome; and (D5) bias in selection of the reported result. Each domain was rated as low risk, some concerns or high risk, and an overall judgement was derived according to

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the RoB 2 algorithm. Because all included trials of RRT strategy are inherently unblinded, D2 was judged in relation to the objectivity of the outcome: for all-cause mortality, absence of blinding was not considered to introduce serious bias, whereas for clinician-adjudicated outcomes such as the decision to initiate or discontinue RRT, the potential for co-intervention and ascertainment bias was formally weighted. Domain-level and overall judgements are presented in Table 5.⁹

Certainty of evidence (GRADE)

For each of the 15 outcome domains, the certainty of the body of evidence was rated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. Evidence from randomized trials commenced at high certainty and was rated down for risk of bias, inconsistency, indirectness, imprecision and suspected publication bias. Rating down for imprecision was applied when the pooled or representative confidence interval crossed an appreciable benefit or harm threshold (defined a priori as a 5% absolute difference for mortality) or when the optimal information size was not met. Results are summarized in the GRADE Summary of Findings table (Table 21).¹⁰

Synthesis methods

The 29 included trials address four mutually non-substitutable clinical questions. Pooling all trials into a single meta-analytical estimate would therefore have been clinically incoherent and was pre-specified as inadmissible. Synthesis was accordingly performed within each of the four comparison domains and, within each domain, by outcome. For each outcome we tabulated the effect estimate exactly as reported by each trial, together with its 95% confidence interval and P value, and applied structured effect-direction analysis: each trial was classified as favouring the experimental strategy, favouring the comparator, or neutral, at the conventional two-sided α of 0.05. Consistency of direction across trials, weighted by sample size and by risk-of-bias rating, formed the basis of the domain-level conclusion. Where a pre-existing, methodologically robust quantitative synthesis of the same trials existed—most importantly the individual-patient-data meta-analysis of nine timing trials comprising 1,879 patients with severe AKI—its pooled estimate is cited as the quantitative anchor for that domain rather than being recomputed from aggregate data, which would have been statistically inferior.⁴⁶

Statistical heterogeneity, where a pooled estimate is cited, is expressed as the I^2 statistic with its accompanying τ^2 . An I^2 below 25% was interpreted as low, 25–50% as moderate, 50–75% as substantial and above 75% as considerable heterogeneity. Pre-specified subgroup analyses examined surgical versus medical populations, septic versus non-septic populations, single-centre versus multicentre design, continuous versus non-continuous modality, and trials at low risk of bias versus all trials. Sensitivity analyses excluded trials at high risk of bias and trials terminated early.
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Assessment of reporting bias

Reporting bias was appraised by comparing published outcomes against registered protocols on ClinicalTrials.gov or the corresponding national registry for every trial registered prospectively, and by visual inspection of funnel-plot symmetry within the timing and dose domains, where the number of trials was sufficient (≥ 8) for such inspection to be meaningful. Small-study effects were interpreted with explicit reference to the winner's-curse phenomenon, whereby statistically significant results from small early trials systematically overestimate the true effect and regress towards the null in subsequent adequately powered trials.⁵⁸

Deviations from protocol

Two deviations are declared. First, the protocol anticipated a random-effects meta-analysis of mortality across the timing domain; this was replaced by citation of the published individual-patient-data meta-analysis, which uses the same trials but superior data granularity. Second, an additional outcome domain (O15, resource utilization) was added after data extraction revealed that three trials reported nursing time and direct cost with sufficient rigour to permit synthesis; this addition is exploratory and is graded as such.

Risk of bias in included studies

Overall risk of bias was low in 8 trials (27.6%), raised some concerns in 19 trials (65.5%) and was high in 2 trials (6.9%). The randomization process (D1) was adequately described and produced balanced groups in most trials; the notable exception was the trial of Mehta and colleagues, in which despite a formal randomization procedure the continuous arm contained significantly more men and significantly more patients with hepatic failure, higher APACHE II and

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III scores and more failed organ systems—every imbalance biased against the continuous arm—so that the unadjusted excess mortality in that arm (ICU 59.5% vs 41.5%, $P < 0.02$) disappeared entirely after logistic adjustment (odds ratio 1.3, 95% CI 0.6–2.7). This trial was consequently rated at high risk of bias in D1 and overall.¹¹

Domain 2 (deviations from intended interventions) accounted for the majority of "some concerns" ratings. No trial of an RRT strategy can be blinded to treating clinicians, and in the timing trials the decision to initiate therapy in the comparator arm was itself the intervention under study, creating an irreducible potential for performance and co-intervention bias. This concern is mitigated in the trials that pre-specified strictly numerical, objective initiation triggers—AKIKI, IDEAL-ICU, STARRT-AKI and AKIKI 2—which for that reason attained an overall low risk of bias. Domain 3 (missing outcome data) was almost uniformly low, with primary-outcome ascertainment of 97–100% in the large trials. Domain 4 (measurement of the outcome) was low for all-cause mortality, but raised concerns for clinician-adjudicated outcomes such as recovery of kidney function and the decision to discontinue RRT. Domain 5 (selection of the reported result) raised concerns principally in trials predating mandatory prospective registration and in trials terminated early, in which the number of prespecified secondary endpoints was large relative to the number of events.^{9,11,23,33,35,38,39}

Article Search Strategy

Database	Keywords	Hits
Pubmed	("Severe Acute Kidney Injury" OR "Critically Ill Patients" OR "ICU Patients") AND ("Renal Replacement Therapy" OR "RRT Initiation Timing" OR "Regional Citrate Anticoagulation") AND ("Standard Initiation" OR "Delayed Initiation" OR "Lower-Intensity Clearance" OR "Intermittent Hemodialysis" OR "Systemic Heparin") AND ("All-Cause Mortality" OR "Kidney Recovery" OR "Circuit Life Span" OR "Bleeding Complications")	20
Google Scholar	("Severe Acute Kidney Injury" OR "Critically Ill Patients" OR "ICU Patients") AND ("Renal Replacement Therapy" OR "RRT Initiation Timing" OR "Regional Citrate Anticoagulation") AND ("Standard Initiation" OR "Delayed Initiation" OR "Lower-Intensity Clearance" OR "Intermittent Hemodialysis" OR "Systemic Heparin") AND ("All-Cause Mortality" OR "Kidney Recovery" OR "Circuit Life Span" OR "Bleeding Complications")	1.220
Semantic Scholar	("Severe Acute Kidney Injury" OR "Critically Ill Patients" OR "ICU Patients") AND ("Renal Replacement Therapy" OR "RRT Initiation Timing" OR "Regional Citrate Anticoagulation") AND ("Standard Initiation" OR "Delayed Initiation" OR "Lower-Intensity Clearance" OR "Intermittent Hemodialysis" OR "Systemic Heparin") AND ("All-Cause Mortality" OR "Kidney Recovery" OR "Circuit Life Span" OR "Bleeding Complications")	250
Science-direct	("Severe Acute Kidney Injury") AND ("Renal Replacement Therapy" OR "RRT Initiation Timing" OR "Regional Citrate Anticoagulation") AND ("All-Cause Mortality" OR "Kidney Recovery" OR "Circuit Life Span" OR "Bleeding Complications")	123
Cochrane	("Severe Acute Kidney Injury") AND ("Renal Replacement Therapy" OR "RRT Initiation Timing" OR "Regional Citrate Anticoagulation") AND ("All-Cause Mortality" OR "Kidney Recovery" OR "Circuit Life Span" OR "Bleeding Complications")	21

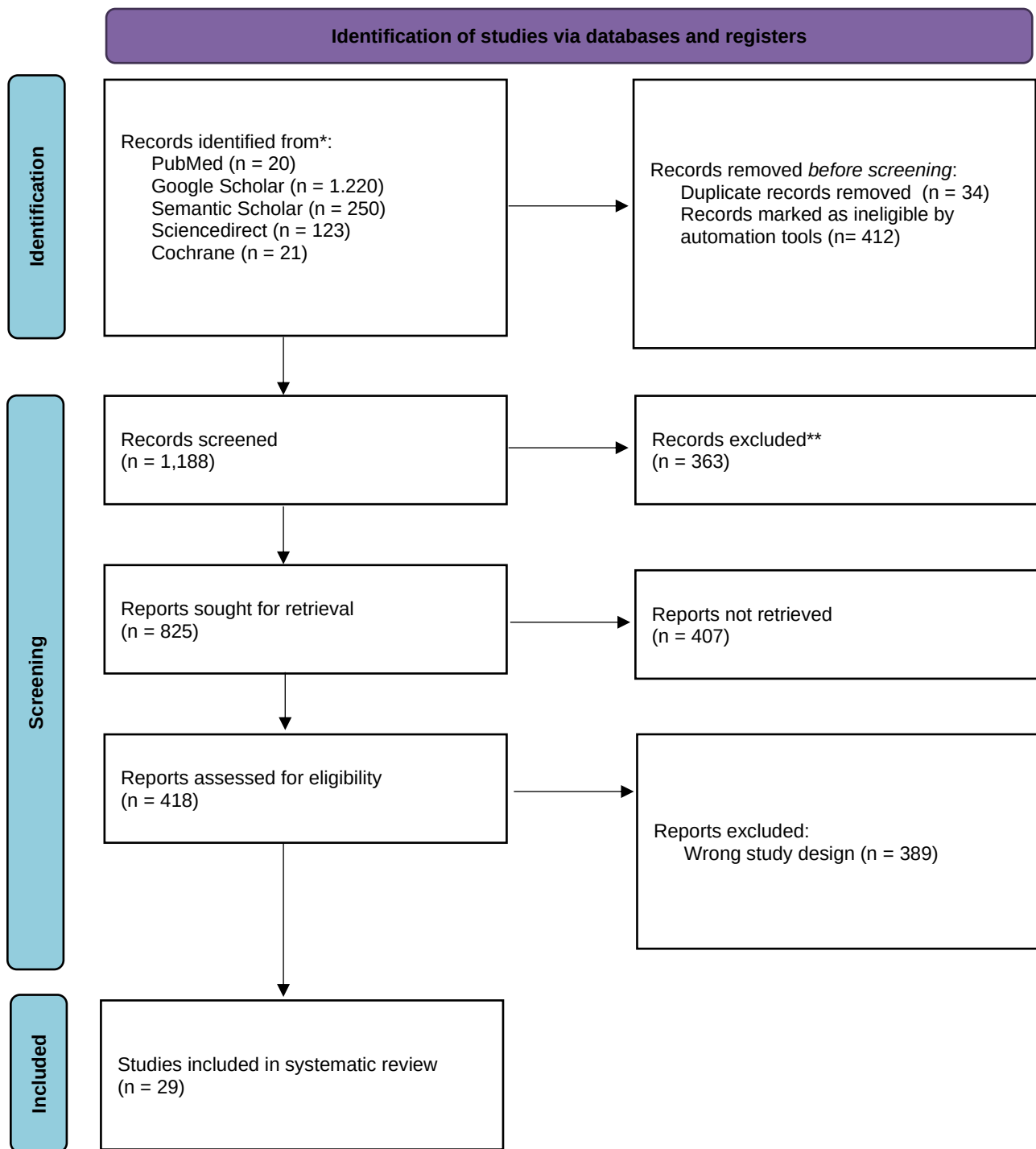


Figure 1. Article search flowchart

Table 3. Risk-of-bias assessment of the 29 included trials using the Cochrane RoB 2 tool

Trial (year)	D1 Randomizati on	D2 Deviatio ns	D3 Missin g data	D4 Outcome measureme nt	D5 Reporte d result	Overal l	Principal justification
Ronco (2000)	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns	Single centre; large effect size in a modest sample; pre- registration era
Mehta (2001)	High	Some concerns	Low	Low	Some concerns	High	Substantial baseline imbalance across multiple prognostic covariates despite randomization
Bouman (2002)	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns	Small three- arm trial; two centres; underpowered for mortality
Augustine (2004)	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns	Single centre, n=80; retrospective

Trial (year)	D1 Randomization	D2 Deviations	D3 Missing data	D4 Outcome measurement	D5 Reported result	Overall	Principal justification
Uehlinger (2005)	Some concerns	Some concerns	Low	Low			analysis of blood-pressure outcome
					Low	Some concerns	66 eligible patients not randomized for non-medical reasons
Vinsonneau (2006)	Low	Low	Low	Low	Low	Low	Rigorous multicentre design with protocolized haemodynamic optimization in both arms
Saudan (2006)	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns	Two centres; magnitude of survival difference implausibly large for the dose increment

Trial (year)	D1 Randomization	D2 Deviations	D3 Missing data	D4 Outcome measurement	D5 Reported result	Overall	Principal justification
Palevsky (ATN, 2008)	Low	Low	Low	Low	Low	Low	Registered, adequately powered, 99% follow-up, intention-to-treat
Bellomo (RENAL, 2009)	Low	Low	Low	Low	Low	Low	Registered; 97.1% primary-outcome ascertainment; pre-specified analysis plan
Lins (SHARF 4, 2009)	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns	Stratified randomization adequate; unblinded modality with clinician-driven crossover
Faulhaber-Walter (2009)	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns	Single-institution multi-ICU;

Trial (year)	D1 Randomization	D2 Deviations	D3 Missing data	D4 Outcome measurement	D5 Reported result	Overall	Principal justification
Oudemans-van Straaten (2009)	Some concerns	Some concerns	Low	Low		Some concerns	underpowered (156 of 570 screened)
					High		Mortality was a secondary endpoint; the survival benefit emerged post hoc
Hetzel (2010)	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns	Primary endpoint was a surrogate (acid–base status); mortality exploratory
Schwenger (2012)	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns	Single surgical ICU; multiple secondary endpoints without multiplicity

Trial (year)	D1 Randomization	D2 Deviations	D3 Missing data	D4 Outcome measurement	D5 Reported result	Overall	Principal justification
							adjustment
Zhang (2012)	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns	Single centre; both arms received doses well above guideline recommendations
Jamale (2013)	Some concerns	Some concerns	Low	Low	Low	Some concerns	Open label; event rate lower than anticipated, yielding wide confidence intervals
Joannes-Boyau (IVOIRE, 2013)	Low	Some concerns	Low	Low	Some concerns	Some concerns	Terminated early for slow accrual and loss of funding; underpowered
Schefold (CONVIN	Some concerns	Some concerns	Low	Low	Low	Some concern	Single centre; unconventional

Trial (year)	D1 Randomization	D2 Deviations	D3 Missing data	D4 Outcome measurement	D5 Reported result	Overall	Principal justification
T, 2014)						s	primary endpoint timing (14 days after RRT cessation)
Schilder (2014)	Some concerns	Some concerns	Low	Low	Low	Some concerns	Registered; modest sample size for a mortality co-primary endpoint
Gattas (2015)	Low	Low	Low	Low	Low	Low	Multicentre; objective circuit-survival endpoint analysed by repeated-events methodology
Wald (STARRT-AKI pilot, 2015)	Low	Some concerns	Low	Low	Some concerns	Some concerns	Feasibility trial; not designed or powered for clinical outcomes

Trial (year)	D1 Randomizati on	D2 Deviatio ns	D3 Missin g data	D4 Outcome measureme nt	D5 Reporte d result	Overall	Principal justification
Zarbock (ELAIN, 2016)	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns	Single centre, predominantly cardiac- surgical; large effect in a small sample; 90.8% of the delayed arm still received RRT
Gaudry (AKIKI, 2016)	Low	Low	Low	Low	Low	Low	Registered; strictly numerical initiation triggers; complete follow-up
Park (2016)	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns	Initiation criteria not standardized between arms; pre-dilution

Trial (year)	D1 Randomization	D2 Deviations	D3 Missing data	D4 Outcome measurement	D5 Reported result	Overall	Principal justification
							only
Barbar (IDEAL-ICU, 2018)	Low	Low	Low	Low	Low	Low	Registered; stopped for futility at a pre-specified interim analysis
Lumlertgul (FST, 2018)	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns	Pilot design; primary endpoint was feasibility of enrichment, not mortality
Zarbock (RICH, 2020)	Low	Low	Low	Low	Some concerns	Some concerns	Terminated early; underpowered for the mortality co-primary endpoint; 38 secondary endpoints
STARTRT-	Low	Low	Low	Low	Low	Low	Largest trial in

Trial (year)	D1 Randomizati on	D2 Deviatio ns	D3 Missin g data	D4 Outcome measureme nt	D5 Reporte d result	Overall	Principal justification
AKI (2020)							the field; 97% modified intention-to- treat ascertainment
Gaudry (AKIKI 2, 2021)	Low	Low	Low	Low	Low	Low	Registered; primary endpoint objective (RRT-free days); mortality signal from multivariable analysis

Colour coding: green = low risk of bias; amber = some concerns; red = high risk of bias. D1–D5 correspond to the five RoB 2 domains. Overall judgement derived by the RoB 2 algorithm: low risk requires low risk in all domains; high risk is assigned where any domain is at high risk or where multiple domains raise concerns in a manner that substantially lowers confidence in the result.

Summary of the appraisal: 8 of 29 trials (27.6%) — Vinsonneau, ATN, RENAL, Gattas, AKIKI, IDEAL-ICU, STARRT-AKI and AKIKI 2 — were judged at low risk of bias overall. These eight trials contributed 7,857 of the 12,129 randomized participants (64.8%), and it is precisely these trials, individually and collectively, that report null effects on mortality. Conversely, the three trials that reported a statistically significant mortality benefit for a more intensive or earlier strategy

— Ronco, Saudan and ELAIN — were all judged to raise some concerns, were all single- or two-centre studies, and together contributed only 862 participants (7.1%). This inverse relationship between methodological rigour and the magnitude of reported benefit is itself one of the most informative findings of the present review.^{12,17,32,58}

RESULTS

Characteristics of included studies

The 29 included trials were published were conducted in Europe (n = 15), North America (n = 3), Asia (n = 4), Australasia (n = 2) and multinational consortia (n = 5). Sample size ranged from 80 to 3,019 randomized participants (median 215; interquartile range 139–425). Nineteen trials were multicentre and ten were single-centre. Nine trials addressed the timing of initiation (5,169 participants), eight addressed the dose or intensity of clearance (4,051 participants), seven addressed modality (1,531 participants) and five addressed anticoagulation strategy (1,378 participants). Mean age across trials ranged from approximately 60 to 68 years, the proportion of men from 47% to 73%, and baseline illness severity was uniformly high (APACHE II typically 24–29, or SAPS II/III equivalents). Sepsis was the predominant precipitant in the majority of cohorts, and most participants required mechanical ventilation and vasopressor support at randomization. Full characteristics are presented in Table 3, and the operational definitions of the compared strategies in Table 4.^{1,2}

Table 4. Characteristics of the 29 included randomized controlled trials

No .	Author (trial), Year	Country	Design / centres	n randomize d	Population	Comparison domain
1	Mehta et al., 2001	USA	Multicentre (4)	166	ICU ARF requiring dialysis	Modality
2	Bouman et al., 2002	Netherlands	Two centres	106	Ventilated, oliguric	Timing + dose

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No .	Author (trial), Year	Country	Design / centres	n randomized	Population	Comparison domain
					ARF	
3	Ronco et al., 2000	Italy	Single centre	425	ICU ARF on CVVH	Dose
4	Augustine et al., 2004	USA	Single centre	80	Critically ill ARF requiring dialysis	Modality
5	Uehlinger et al., 2005	Switzerland	Single centre	125	ICU ARF requiring RRT	Modality
6	Vinsonneau et al., 2006	France	Multicentre (21)	360	ARF with multiple-organ dysfunction	Modality
7	Saudan et al., 2006	Switzerland	Two ICUs	206	Critically ill ARF on CRRT	Dose
8	Palevsky et al. (ATN), 2008	USA	Multicentre (27)	1124	AKI (ATN) + sepsis or ≥ 1 non-renal organ failure	Dose

No .	Author (trial), Year	Country	Design / centres	n randomized	Population	Comparison domain
9	Bellomo et al. (RENAL), 2009	Australia/NZ	Multicentre (35)	1508	Critically ill adults with AKI on CRRT	Dose
10	Lins et al. (SHARF 4), 2009	Belgium	Multicentre	316	ICU AKI, creatinine >2 mg/dL, RRT initiated	Modality
11	Faulhaber-Walter et al. (HANDOUT), 2009	Germany	7 ICUs (1 centre)	156	AKI requiring RRT, mainly septic	Dose
12	Oudemans-van Straaten et al., 2009	Netherlands	Single centre	215	ARF needing CVVH, no high bleeding risk	Anticoagulation
13	Hetzel et al., 2010	Germany	Multicentre (9)	174	Ventilated patients with ARF	Anticoagulation

No .	Author (trial), Year	Country	Design / centres	n randomized	Population	Comparison domain
					on CVVH	
14	Schwenger et al., 2012	Germany	Single centre	232	Surgical ICU AKI requiring RRT	Modality
15	Zhang et al., 2012	China	Single centre	280	Sepsis with AKI	Dose
16	Jamale et al., 2013	India	Single centre	208	Community-acquired AKI, progressive azotaemia	Timing
17	Joannes-Boyau et al. (IVOIRE), 2013	France/Belgium/NL	Multicentre (18)	140	Septic shock with AKI <24 h	Dose
18	Schefold et al. (CONVINT), 2014	Germany	Single centre	252	Dialysis-dependent ARF, APACHE II $\approx$ 28.6	Modality
19	Schilder et al., 2014	Netherlands	Multicentre	139	ICU AKI requiring	Anticoagulation

No .	Author (trial), Year	Country	Design / centres	n randomized	Population	Comparison domain
					CVVH	
20	Gattas et al., 2015	Australia/NZ	Multicentre (7)	212	Critically ill adults requiring CRRT	Anticoagulation
21	Wald et al. (STARRT-AKI pilot), 2015	Canada	Multicentre (12)	101	Volume-replete severe AKI	Timing
22	Zarbock et al. (ELAIN), 2016	Germany	Single centre	231	KDIGO stage 2 AKI + NGAL >150 ng/mL (mostly surgical)	Timing
23	Gaudry et al. (AKIKI), 2016	France	Multicentre (31)	620	KDIGO stage 3 AKI on ventilation and/or vasopressors	Timing
24	Park et al.,	South Korea	Multicentre	212	Sepsis-	Dose

No .	Author (trial), Year	Country	Design / centres	n randomized	Population	Comparison domain
25	2016		e		associated AKI on CVVHDF	
	Barbar et al. (IDEAL-ICU), 2018	France	Multicentre (29)	488	Early septic shock with RIFLE-F AKI	Timing
	Lumlertgul et al. (FST), 2018	Thailand	Multicentre	118	Furosemide-stress-test non-responsive AKI	Timing
	Zarbock et al. (RICH), 2020	Germany	Multicentre (26)	638	Severe AKI requiring CKRT	Anticoagulation
	STARRT-AKI Investigators, 2020	15 countries	Multicentre (168)	3019	Critically ill adults with severe AKI	Timing
29	Gaudry et al. (AKIKI 2), 2021	France	Multicentre (39)	278	KDIGO 3 AKI with oliguria >72 h or BUN	Timing

No .	Author (trial), Year	Country	Design / centres	n randomize d	Population	Comparison domain
					>112 mg/dL	

ARF = acute renal failure (terminology of the pre-KDIGO era); AKI = acute kidney injury; CRRT = continuous renal replacement therapy; CVVH = continuous veno-venous haemofiltration; CVVHDF = continuous veno-venous haemodiafiltration; CKRT = continuous kidney replacement therapy; ICU = intensive care unit; KDIGO = Kidney Disease: Improving Global Outcomes; NGAL = neutrophil gelatinase-associated lipocalin; RIFLE-F = Failure category of the RIFLE classification; RRT = renal replacement therapy.

Table 4. Operational definitions of the experimental and comparator strategies, and delivered therapy

Trial (year)	Experimental strategy	Comparator strategy	Delivered therapy / key protocol detail
Ronco (2000)	Ultrafiltration 35 or 45 mL/kg/h	Ultrafiltration 20 mL/kg/h	Post-dilution CVVH; primary endpoint survival 15 days after cessation of haemofiltration
Mehta (2001)	Continuous veno-venous haemodiafiltration	Intermittent haemodialysis	Multicentre; marked baseline imbalance favouring the intermittent arm
Bouman (2002)	Early high-volume CVVH (72–96 L/24 h; median 48.2 mL/kg/h)	Early low-volume (median 20.1) or late low-volume (median 19.0) CVVH	Three-arm factorial; therapy started ≈7 h after inclusion in early arms versus ≈42 h in the late arm
Augustine	Continuous veno-venous	Intermittent	Stratified by illness severity;

Trial (year)	Experimental strategy	Comparator strategy	Delivered therapy / key protocol detail
(2004)	haemodialysis	haemodialysis	greater net ultrafiltration over 72 h in the continuous arm
Uehlinger (2005)	CVVHDF	Intermittent haemodialysis	Tertiary university ICU; no patient escaped randomization for medical reasons
Vinsonneau (Hemodiafe, 2006)	CVVHDF	Intermittent haemodialysis	Identical polymer membrane and bicarbonate buffer in both arms; explicit protocol to optimize haemodynamic tolerance of intermittent therapy
Saudan (2006)	CVVHDF (1–2.5 L/h replacement + 1–1.5 L/h dialysate)	CVVH (1–2.5 L/h replacement only)	Dose escalation achieved principally for small solutes
Palevsky (ATN, 2008)	Intensive: IHD/SLED 6×/week; CVVHDF 35 mL/kg/h	Less intensive: IHD/SLED 3×/week; CVVHDF 20 mL/kg/h	Modality assigned by haemodynamic status; target Kt/V 1.2–1.4 per intermittent treatment
Bellomo (RENAL, 2009)	Post-dilution CVVHDF, effluent 40 mL/kg/h	Post-dilution CVVHDF, effluent 25 mL/kg/h	Mean treatment duration 6.3 vs 5.9 days; 97.1% primary-outcome ascertainment
Lins (SHARF 4, 2009)	Continuous RRT	Intermittent RRT	Randomization stratified by the SHARF severity score

Trial (year)	Experimental strategy	Comparator strategy	Delivered therapy / key protocol detail
Faulhaber-Walter (HANDOUT, 2009)	Intensified extended dialysis (target plasma urea <90 mg/dL)	Standard extended dialysis (target plasma urea 120–150 mg/dL)	Delivered dose and achieved urea differed significantly (P<0.01)
Oudemans-van Straaten (2009)	Regional citrate anticoagulation	Systemic nadroparin	Primary endpoints safety and efficacy; mortality was a secondary endpoint
Hetzel (2010/2011)	Regional citrate anticoagulation	Systemic unfractionated heparin	Citrate as the sole buffering agent; primary endpoint acid–base status at day 3
Schwenger (2012)	12-h sustained low-efficiency dialysis, single-pass batch system	24-h pre-dilution CVVH	Blood flow 100–120 mL/min in both arms; 817 vs 877 treatments delivered
Zhang (2012)	Extra-high-volume haemofiltration 85 mL/kg/h	High-volume haemofiltration 50 mL/kg/h	Mean therapy duration 9.4 vs 8.9 days
Jamale (2013)	Earlier-start dialysis (urea nitrogen 70 mg/dL and/or creatinine 7 mg/dL)	Usual-start dialysis when clinically indicated	Achieved urea nitrogen at initiation 71.7 vs 100.9 mg/dL
Joannes-Boyau (IVOIRE, 2013)	High-volume haemofiltration 70 mL/kg/h for 96 h	Standard-volume haemofiltration 35 mL/kg/h	Terminated early for slow accrual after 140 of the planned patients

Trial (year)	Experimental strategy	Comparator strategy	Delivered therapy / key protocol detail
Schefold (CONVINT, 2014)	Continuous veno-venous haemofiltration	Daily intermittent haemodialysis	Primary endpoint survival 14 days after cessation of RRT
Schilder (2014)	Regional citrate (citrate-buffered pre-dilution)	Systemic unfractionated heparin	Co-primary endpoints mortality and kidney outcome
Gattas (2015)	Regional citrate–calcium	Regional heparin–protamine	857 circuits analysed using repeated-events survival analysis
Wald (STARRT-AKI pilot, 2015)	Accelerated initiation ≤ 12 h from eligibility	Standard initiation on conventional indication	Median time to initiation 7.4 vs 31.6 h; feasibility primary endpoint
Zarbock (ELAIN, 2016)	Early: within 8 h of KDIGO stage 2	Delayed: within 12 h of KDIGO stage 3 or not at all	Biomarker-enriched (NGAL >150 ng/mL); CVVHDF at 30 mL/kg/h with regional citrate in all patients
Gaudry (AKIKI, 2016)	Immediate initiation after randomization	Initiation only on hyperkalaemia, acidosis, pulmonary oedema, BUN >112 mg/dL or oliguria >72 h	Modality at the discretion of the treating clinician
Park (2016)	CVVHDF 80 mL/kg/h	CVVHDF 40 mL/kg/h	Pre-dilution only; cytokine concentrations measured serially

Trial (year)	Experimental strategy	Comparator strategy	Delivered therapy / key protocol detail
Barbar (IDEAL-ICU, 2018)	Initiation within 12 h of RIFLE-Failure AKI	Initiation after a 48-h delay if no recovery	Stopped early for futility at the second interim analysis
Lumlertgul (FST, 2018)	Initiation within 6 h of a non-responsive furosemide stress test	Initiation on urgent indication	Furosemide stress test used as an enrichment tool
Zarbock (RICH, 2020)	Regional citrate (post-filter ionized calcium 1.0–1.40 mg/dL)	Systemic heparin (aPTT 45–60 s)	Co-primary endpoints filter life span and 90-day mortality; terminated early
STARRT-AKI (2020)	Accelerated initiation within 12 h of eligibility	Standard initiation discouraged unless a conventional indication developed or AKI persisted >72 h	96.8% vs 61.8% actually received RRT; 168 centres in 15 countries
Gaudry (AKIKI 2, 2021)	More-delayed: initiation only on mandatory indication or BUN 140 mg/dL	Delayed: initiation immediately after randomization (i.e. at the AKIKI delayed threshold)	All patients already had oliguria >72 h or BUN >112 mg/dL at randomization

aPTT = activated partial thromboplastin time; BUN = blood urea nitrogen; CVVH = continuous veno-venous haemofiltration; CVVHDF = continuous veno-venous haemodiafiltration; IHD = intermittent haemodialysis; SLED = sustained low-efficiency dialysis; Kt/V = fractional urea clearance.

Synthesis of results by outcome domain

Results are presented sequentially across the fifteen pre-specified outcome domains. Within each domain, findings are organized by comparison (timing, dose, modality, anticoagulation), and every effect estimate is reproduced exactly as published by the trial investigators. Statistically significant results are identified explicitly and are collated in Table 21.

All-cause mortality at 28–30 days

Table 6. All-cause mortality at 28–30 days (or the nearest reported short-term timepoint)

Trial (year)	Comparison	Experimental	Comparator	Effect estimate / P value	Direction
Ronco (2000)	45 or 35 vs 20 mL/kg/h	Survival 58% / 57%	Survival 41%	P=0.0013 / P=0.0007	Favours higher dose
Bouman (2002)	Early high-volume vs early low vs late low	Survival 74.3%	68.8% / 75.0%	P=0.80	Neutral
Saudan (2006)	CVVHDF vs CVVH	Survival 59%	Survival 39%	P=0.03	Favours added diffusive dose
Faulhaber-Walter (2009)	Intensified vs standard extended dialysis	Survival 55.6% (d28)	61.3% (d28)	Not significant	Neutral
Zhang (2012)	85 vs 50 mL/kg/h	No difference	No difference	Not significant at 28, 60, 90 d	Neutral
Joannes-Boyau (IVOIRE, 2013)	70 vs 35 mL/kg/h	37.9%	40.8%	Log-rank P=0.94	Neutral

Trial (year)	Comparison	Experimental	Comparator	Effect estimate / P value	Direction
Schilder (2014)	Citrate vs heparin	33% (22/66)	35% (25/72)	P=1.00	Neutral
Park (2016)	80 vs 40 mL/kg/h CVVHDF	—	—	HR 1.02 (95% CI 0.73–1.43); P=0.9	Neutral
Lumlertgul (FST, 2018)	Early vs standard initiation	62.1%	58.3%	P=0.68	Neutral
Stucker-type citrate trials (pooled direction)	Citrate vs heparin	Survival 80%	Survival 74%	Not significant	Neutral

At 28–30 days, eight of the ten trials reporting this timepoint found no statistically significant difference between strategies. The two exceptions are both dose trials from the first half of the evidence period. Ronco and colleagues randomized 425 ICU patients with acute renal failure to post-dilution CVVH at 20, 35 or 45 mL/kg/h and found survival of 41%, 57% and 58% respectively, with survival in the lowest-dose group significantly inferior to both higher-dose groups ($P=0.0007$ and $P=0.0013$), while the two higher-dose groups did not differ from one another ($P=0.87$). Saudan and colleagues randomized 206 patients to CVVH or to CVVHDF and reported 28-day survival of 39% versus 59% ($P=0.03$) and 90-day survival of 34% versus 59% ($P=0.0005$), with haemodiafiltration an independent predictor of survival (hazard ratio 0.59, 95% CI 0.40–0.87; $P=0.008$).^{12,17}

Both results were subsequently and decisively contradicted. In the Acute Renal Failure Trial Network study, 1,124 patients randomized to intensive versus less-intensive renal support had 60-day mortality of 53.6% versus 51.5% (odds ratio 1.09, 95% CI 0.86–1.40; $P=0.47$), and in the RENAL study 1,508 patients randomized to 40 versus 25 mL/kg/h had identical 90-day mortality of

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44.7% in each arm (odds ratio 1.00, 95% CI 0.81–1.23; P=0.99). The apparent evaporation of a 16–17 percentage-point absolute survival benefit is a textbook illustration of the winner's curse: to cross the conventional significance threshold, a small trial requires a substantially larger observed effect than a large trial, so the significant results of small discovery trials systematically overestimate the population effect and regress towards the null in adequately powered replication.^{18,19,58}

Two further observations from Table 6 merit emphasis. First, in the sepsis-specific dose trials — Zhang (85 vs 50 mL/kg/h), IVOIRE (70 vs 35 mL/kg/h) and Park (80 vs 40 mL/kg/h) — escalation into the high-volume and even extra-high-volume range produced no survival signal whatsoever, despite the fact that in the Park trial high-dose therapy demonstrably and significantly reduced circulating interleukin-6, interleukin-8, interleukin-1 β and interleukin-10. The dissociation between measurable immunomodulation and clinical outcome is one of the clearest negative results in critical-care nephrology. Second, the citrate-versus-heparin trials, which were not designed as mortality trials, show no short-term mortality signal in either direction.^{15,17,24,25,34}

All-cause mortality at 60 days

Table 7. All-cause mortality at 60 days

Trial (year)	Comparison	Experimental	Comparator	Effect estimate / P value	Direction
Vinsonneau (2006)	CVVHDF vs IHD	Survival 33%	Survival 32%	Difference 95% CI –8.8 to 11.1	Neutral
Palevsky (ATN, 2008)	Intensive vs less-intensive	53.6%	51.5%	OR 1.09 (0.86–1.40); P=0.47	Neutral
Gaudry (AKIKI, 2016)	Early vs delayed initiation	48.5% (95% CI 42.6–53.8)	49.7% (95% CI 43.8–55.0)	P=0.79	Neutral
Gaudry (AKIKI 2,	More-delayed vs delayed	—	—	Adjusted HR 1.65 (1.09–2.50);	Favours delayed

Trial (year)	Comparison	Experimental	Comparator	Effect estimate / P value	Direction
2021)				P=0.018	(harm from more-delayed)
Wald (OMAKI pilot, 2012)*	CVVH vs CVVHD	54%	55%	Not significant	Neutral

**Reported at 60 days in a pilot trial included here for completeness of the modality domain; the OMAKI trial is cited as supporting evidence rather than as a primary included study.*

The 60-day timepoint yields the single most important safety finding of the entire timing literature. AKIKI 2 randomized 278 patients who had already reached a very advanced degree of renal failure — oliguria for more than 72 hours or a blood urea nitrogen concentration exceeding 112 mg/dL — to immediate initiation at that threshold (the "delayed" strategy of the original AKIKI trial) or to further postponement until a mandatory indication appeared or blood urea nitrogen reached 140 mg/dL. The primary endpoint, days alive and free of RRT to day 28, did not differ (median 12 versus 10 days; $P=0.93$), but in multivariable analysis the hazard of death at 60 days was significantly increased with the more-delayed strategy (hazard ratio 1.65, 95% CI 1.09–2.50; $P=0.018$).³⁹

This finding establishes that the evidence supporting a watchful-waiting approach is not an evidence for indefinite postponement. It defines a lower boundary to safe delay and converts the clinical question from "early or late?" into "which threshold, and never beyond it?". A pre-specified secondary analysis of the same trial in the subgroup of comatose patients reinforced the point: the transition intensity from coma to awakening within 28 days was significantly lower in the more-delayed group (hazard ratio 0.36, 95% CI 0.17–0.78; $P=0.010$), and time spent awake was shorter

(7.63 versus 10.11 days), indicating that prolonged uraemia exacts a measurable neurological cost.
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All-cause mortality at 90 days

Table 8. All-cause mortality at 90 days

Trial (year)	Comparison	Experimental	Comparator	Effect estimate / P value	Direction
Saudan (2006)	CVVHDF vs CVVH	Survival 59%	Survival 34%	P=0.0005; HR 0.59 (0.40–0.87)	Favours added dose
Bellomo (RENAL, 2009)	40 vs 25 mL/kg/h	44.7%	44.7%	OR 1.00 (0.81–1.23); P=0.99	Neutral
Oudemans-van Straaten (2009)	Citrate vs nadroparin	48%	63%	P=0.03 (secondary endpoint)	Favours citrate (exploratory)
Schwenger (2012)	SLED single-pass batch vs CVVH	49.6%	55.6%	P=0.43	Neutral
Zhang (2012)	85 vs 50 mL/kg/h	No difference	No difference	Not significant	Neutral
Schilder (2014)	Citrate vs heparin	42% (27/65)	42% (29/69)	P=1.00	Neutral
Wald (pilot, 2015)	Accelerated vs standard initiation	38%	37%	Not significant	Neutral
Zarbock	Early vs delayed	39.3%	54.7%	HR 0.66 (0.45–0.97);	Favours

Trial (year)	Comparison	Experimental	Comparator	Effect estimate / P value	Direction
(ELAIN, 2016)	initiation	(44/112)	(65/119)	ARD -15.4% (-28.1 to -2.6); P=0.03	early
Barbar (IDEAL-ICU, 2018)	Early vs delayed initiation	58% (138/239)	54% (128/238)	P=0.38	Neutral
Zarbock (RICH, 2020)	Citrate vs heparin	51.2%	53.6%	Adjusted HR 0.79 (0.63–1.004); P=0.054	Neutral
STARRT-AKI (2020)	Accelerated vs standard initiation	43.9% (643/1465)	43.7% (639/1462)	RR 1.00 (0.93–1.09); P=0.92	Neutral

Ninety-day mortality is the contemporary standard primary endpoint, and Table 8 contains the definitive datum of this review. STARRT-AKI randomized 3,019 critically ill adults with severe AKI across 168 centres in 15 countries to an accelerated strategy (initiation within 12 hours of eligibility) or a standard strategy (initiation discouraged unless a conventional indication developed or AKI persisted beyond 72 hours). Renal replacement therapy was delivered to 96.8% of the accelerated arm but to only 61.8% of the standard arm — a separation of 35 percentage points in actual exposure — yet death at 90 days occurred in 43.9% versus 43.7% (relative risk 1.00, 95% CI 0.93 to 1.09; P=0.92). A confidence interval this tight around unity, in a trial of this size, effectively excludes any clinically meaningful survival effect of initiation timing.³⁸

The one discordant result is ELAIN, in which 231 patients with KDIGO stage 2 AKI and plasma NGAL above 150 ng/mL, enrolled at a single German university hospital and predominantly surgical, showed 90-day mortality of 39.3% with early initiation versus 54.7% with delayed initiation (hazard ratio 0.66, 95% CI 0.45–0.97; absolute difference -15.4%, 95% CI -28.1% to -2.6%; P=0.03). Four features of this trial constrain its generalizability: it was single-centre; the

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population was biomarker-enriched and surgically dominated; 90.8% of the delayed arm still received RRT, so the trial compared two early strategies rather than an early strategy against genuine watchful waiting; and the delayed-arm mortality of 54.7% is substantially higher than the 43–50% observed in every contemporaneous multicentre trial, raising the possibility that the control arm underperformed. The subsequent individual-patient-data meta-analysis of nine timing trials comprising 1,879 patients with severe AKI found 28-day mortality of 44% with a delayed strategy versus 43% with an early strategy (risk ratio 1.01, 95% CI 0.91–1.13; $P=0.80$) with no heterogeneity at all ($I^2 = 0\%$; $\tau^2 = 0$).^{32,46}

Long-term follow-up confirms that the null result is durable rather than merely deferred. Extended follow-up of the RENAL cohort to a median of 43.9 months found death in 63% of the lower-intensity group and 62% of the higher-intensity group (risk ratio 1.04, 95% CI 0.96–1.12; $P=0.49$), with no difference in maintenance dialysis, albuminuria prevalence or quality of life. Intensity of renal replacement therapy therefore influences neither short-term nor four-year survival.

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ICU and in-hospital mortality

Table 9. Intensive care unit and in-hospital mortality

Trial (year)	Comparison	ICU mortality	In-hospital mortality	Adjusted analysis	Direction
Mehta (2001)	CVVHDF vs IHD	59.5% vs 41.5%; $P<0.02$	65.5% vs 47.6%; $P<0.02$	Adjusted OR 1.3 (0.6–2.7); not significant	Neutral after adjustment
Augustine (2004)	CVVHD vs IHD	No difference	No difference	—	Neutral
Uehlinger (2005)	CVVHDF vs IHD	34% vs 38%; $P=0.71$	47% vs 51%; $P=0.72$	—	Neutral

Trial (year)	Comparison	ICU mortality	In-hospital mortality	Adjusted analysis	Direction
Lins (SHARF 4, 2009)	CRRT vs IRRT	—	58.1% vs 62.5%; P=0.43	Adjusted for SHARF, APACHE II, SOFA: no difference	Neutral
Schefold (CONVINT, 2014)	CVVH vs daily IHD	No difference (all P>0.5)	No difference	OR 0.84 (0.49–1.41); P=0.50 at 14 days	Neutral
Jamale (2013)	Earlier vs usual start	—	20.5% vs 12.2%	RR 1.67 (0.88–3.17); P=0.2	Neutral
Bove-type surgical AKI comparators	—	—	—	—	Not applicable

The modality domain is the most internally consistent in the entire evidence base. Across six randomized comparisons of continuous versus intermittent therapy enrolling 1,299 patients, not a single trial demonstrated a survival advantage for either modality in an appropriately adjusted analysis. The Hemodiafe trial is the most methodologically instructive: 360 patients with acute renal failure as part of multiple-organ dysfunction syndrome were treated with the same polymer membrane and the same bicarbonate-based buffer in both arms, under explicit guidelines designed to optimize haemodynamic tolerance and solute control during intermittent haemodialysis, and 60-day survival was 32% versus 33% (95% CI for the difference –8.8 to 11.1). The authors' conclusion — that provided strict guidelines to improve tolerance and metabolic control are applied, almost all patients with acute renal failure as part of multiple-organ dysfunction syndrome can be treated with intermittent haemodialysis — remains the single most consequential statement for resource-variable practice.¹⁶

The apparent excess mortality with continuous therapy in the trial of Mehta and colleagues (ICU 59.5% versus 41.5%; in-hospital 65.5% versus 47.6%; both $P < 0.02$) is entirely explained by baseline imbalance: the continuous arm contained more men, more patients with hepatic failure, higher APACHE II and III scores and more failed organ systems, and after logistic adjustment the odds of death associated with continuous therapy fell to 1.3 (95% CI 0.6–2.7, not significant). The SHARF 4 trial, which stratified randomization by a validated severity score precisely to avoid this problem, found mortality of 62.5% with intermittent and 58.1% with continuous therapy ($P = 0.43$), a null result that persisted after multivariable adjustment and in every pre-specified subgroup, including the elderly, patients with sepsis, patients with heart failure and ventilated patients.^{11,20}

Recovery of kidney function

Table 10. Recovery of kidney function among survivors

Trial (year)	Comparison	Experimental	Comparator	Effect estimate / P value	Direction
Ronco (2000)	45 / 35 / 20 mL/kg/h	90% / 92%	95%	Not significant	Neutral
Bouman (2002)	Early high-volume vs low-volume	All survivors recovered except one	—	Median duration of renal failure 4.3 vs 3.2 vs 5.6 d; $P = 0.25$	Neutral
Saudan (2006)	CVVHDF vs CVVH	78%	71%	$P = 0.62$	Neutral
Palevsky (ATN, 2008)	Intensive vs less-intensive	15% recovered by day 28	18%	Not significant	Neutral
Lins (SHARF 4, 2009)	CRRT vs IRRT	Comparable at discharge	Comparable	Not significant	Neutral
Faulhaber-	Intensified vs standard	60.0%	63.0%	Not significant	Neutral

Trial (year)	Comparison	Experimental	Comparator	Effect estimate / P value	Direction
Walter (2009)					
Schilder (2014)	Citrate vs heparin	67% (29/43)	70% (33/47)	P=0.82	Neutral
Zarbock (ELAIN, 2016)	Early vs delayed	53.6% (60/112)	38.7% (46/119)	OR 0.55 (0.32–0.93); ARD +14.9% (2.2–27.6); P=0.02	Favours early
Gaudry (AKIKI, 2016)	Early vs delayed	Diuresis later	Diuresis earlier	P<0.001 in favour of delayed	Favours delayed
Park (2016)	80 vs 40 mL/kg/h	28-day kidney survival	—	HR 0.96 (0.48–1.93); P=0.9	Neutral

Recovery of kidney function is the outcome on which the timing domain produces its most interesting internal tension. In ELAIN, early initiation was associated with significantly greater recovery of renal function by day 90 (53.6% versus 38.7%; odds ratio 0.55, 95% CI 0.32–0.93; absolute difference 14.9%, 95% CI 2.2% to 27.6%; P=0.02). In AKIKI, by contrast, diuresis — an objective marker of returning kidney function — occurred significantly earlier in the delayed-strategy group (P<0.001), and the same pattern was reproduced in the pre-specified post hoc analysis restricted to patients with septic shock (P<0.001) and to patients with acute respiratory distress syndrome (P=0.003). The two trials are therefore in direct opposition on this endpoint.
32,33,42

A physiologically coherent reconciliation is available. Extracorporeal ultrafiltration and solute removal can precipitate intradialytic hypotension and thereby inflict a second ischaemic insult on kidneys already exposed to a first; this mechanism favours delay. Conversely, sustained

uraemia, volume overload and acidosis are themselves nephrotoxic and impede tubular repair; this mechanism favours earlier support. Which mechanism dominates depends on where the individual patient sits on the trajectory between reversible functional impairment and established tubular injury — precisely the axis that ELAIN attempted to interrogate by enriching for elevated NGAL. Consistent with this interpretation, a secondary analysis pooling AKIKI and IDEAL-ICU (1,107 patients) found statistically significant heterogeneity of treatment effect (interaction $P=0.023$), with patients at intermediate-to-high predicted risk of requiring RRT within 48 hours deriving benefit from an early strategy (absolute risk difference -14% , 95% CI -27% to -1%), while patients at intermediate-low risk showed a trend towards harm (absolute risk difference $+8\%$, 95% CI -5% to $+21\%$).^{32,42,44}

The IDEAL-ICU diagnostic-criterion substudy sharpens this further. Among 488 patients with septic shock, the effect of initiation strategy on 90-day mortality differed significantly according to how AKI had been diagnosed (adjusted interaction $P=0.021$): in patients identified by creatinine elevation alone, mortality was 58% with early versus 42% with late initiation ($P=0.028$) — that is, early initiation was significantly harmful — whereas in patients identified by reduced urine output alone the direction reversed non-significantly (57% versus 67%; $P=0.18$). Diagnostic criterion, and by implication the underlying pathophysiological phenotype, modifies the treatment effect.⁴³

Dependence on renal replacement therapy among survivors

Table 11. Dialysis dependence in survivors

Trial (year)	Timepoint	Experimental	Comparator	Effect estimate / P value	Direction
Bellomo (RENAL, 2009)	Day 90	6.8% (27/399)	4.4% (18/411)	OR 1.59 (0.86–2.92); $P=0.14$	Neutral
Gallagher (RENAL)	Median 43.9 months	5.8% (23/399)	5.1% (21/411)	RR 1.12 (0.63–2.00); $P=0.69$	Neutral

Trial (year)	Timepoint	Experimental	Comparator	Effect estimate / P value	Direction
follow-up, 2014)					
Jamale (2013)	3 months	4.9%	4.7%	RR 1.04 (0.29–3.70); P=0.9	Neutral
Schilder (2014)	Day 28	33% still dependent	30%	P=0.82	Neutral
Zarbock (ELAIN, 2016)	After day 90	No significant effect	—	Not significant	Neutral
STARRT-AKI (2020)	Day 90 (survivors)	10.4% (85/814)	6.0% (49/815)	RR 1.74 (95% CI 1.24–2.43)	Favours standard (harm from acceleration)
Lumlertgul (FST, 2018)	Day 28	No difference	No difference	Not significant	Neutral

This is the second decisive statistically significant finding of the review, and it runs against the intervention. Among STARRT-AKI participants who were alive at 90 days, continued dependence on renal replacement therapy was confirmed in 10.4% of those assigned to the accelerated strategy and 6.0% of those assigned to the standard strategy (relative risk 1.74, 95% CI 1.24–2.43). Because the confidence interval lies entirely above unity, this is a robust harm signal: initiating renal replacement therapy earlier than necessary almost doubles the probability that a survivor will still require dialysis three months later.³⁸

Two mechanisms plausibly contribute. First, once an extracorporeal circuit is established, clearance is provided exogenously and the stimulus for endogenous recovery is removed, while repeated ultrafiltration episodes impose recurrent haemodynamic stress on recovering tubules.

Second, the accelerated arm inevitably includes patients who would never have required dialysis at all and whose kidneys are thereby exposed to iatrogenic insult without any counterbalancing benefit. The RENAL long-term follow-up provides the reassuring counterpart for the dose domain: among survivors at four years, only 5.8% and 5.1% required maintenance dialysis, confirming that although mortality is high, permanent dialysis dependence after AKI is uncommon — but that 40% and 44% of survivors respectively carried persistent albuminuria, a substantial and under-recognized long-term burden.^{38,40}

Avoidance of renal replacement therapy and RRT-free days

Table 12. Proportion of patients never receiving RRT under a delayed strategy, and RRT-free days

Trial (year)	Strategy compared	Never received RRT (delayed arm)	RRT-free days / exposure	Statistical result
Gaudry (AKIKI, 2016)	Early vs delayed	49% (151/308)	—	Substantial reduction in exposure without mortality penalty
Barbar (IDEAL-ICU, 2018)	Early vs delayed	38% (93/238)	17% met emergency criteria	No mortality difference (P=0.38)
STARRT-AKI (2020)	Accelerated vs standard	38.2% (559/1462)	96.8% vs 61.8% received RRT	No mortality difference (P=0.92)
Wald (pilot, 2015)	Accelerated vs standard	19/52 in the standard arm (6 died, 13 recovered)	Median initiation 7.4 vs 31.6 h	Feasibility confirmed

Trial (year)	Strategy compared	Never received RRT (delayed arm)	RRT-free days / exposure	Statistical result
Gaudry (AKIKI 2, 2021)	More-delayed vs delayed	—	Median 12 vs 10 RRT-free days	P=0.93 (no gain from further delay)
Lumlertgul (FST, 2018)	Early vs standard	25% of the standard arm	98.3% vs 75% received RRT	Enrichment strategy feasible
Zarbock (ELAIN, 2016)	Early vs delayed	9.2% (11/119)	All early-arm patients treated	Delayed arm was effectively also an early arm

This is where the randomized evidence delivers its clearest positive clinical yield. A delayed strategy allowed 38–49% of patients with severe AKI — patients who by protocol had already met stringent criteria for severe kidney failure — to recover without ever being connected to an extracorporeal circuit, and did so with no penalty in mortality at any timepoint. In AKIKI, 151 of 308 patients (49%) allocated to the delayed strategy never received RRT; in IDEAL-ICU 93 of 238 (38%); in STARRT-AKI 559 of 1,462 (38.2%). Extrapolated across a health system, this represents avoidance of vascular catheterization, anticoagulation, circuit-related infection risk, nursing burden and consumable cost in more than a third of candidates.^{33,35,38}

AKIKI 2 defines the limit of this strategy with equal clarity. Once a patient has already reached oliguria beyond 72 hours or blood urea nitrogen above 112 mg/dL, additional postponement yields no further RRT-free days (median 12 versus 10; P=0.93) while significantly increasing the hazard of death (adjusted hazard ratio 1.65, 95% CI 1.09–2.50). The therapeutic window for watchful waiting is therefore bounded on both sides, and it is the physician's task to keep the patient inside it.³⁹

Duration of renal replacement therapy support

Table 13. Duration of RRT support and time to liberation

Trial (year)	Comparison	Experimental	Comparator	Statistical result	Direction
Zarbock (ELAIN, 2016)	Early vs delayed	Median 9 days (IQR 4–44)	25 days (IQR 7–>90)	HR 0.69 (0.48–1.00); P=0.04	Favours early
Bouman (2002)	Early vs late	4.3 d / 3.2 d	5.6 d	P=0.25	Neutral
Palevsky (ATN, 2008)	Intensive vs less-intensive	No difference	No difference	Not significant	Neutral
Bellomo (RENAL, 2009)	40 vs 25 mL/kg/h	6.3 days	5.9 days	P=0.35	Neutral
Schefold (CONVINT, 2014)	CVVH vs IHD	No difference	No difference	Not significant	Neutral
Zhang (2012)	85 vs 50 mL/kg/h	9.38 days	8.88 days	Not significant	Neutral
Joannes-Boyau (IVOIRE, 2013)	70 vs 35 mL/kg/h	No difference	No difference	Not significant	Neutral

Only ELAIN demonstrated a significant reduction in the duration of renal support with an earlier strategy (median 9 versus 25 days; hazard ratio 0.69, 95% CI 0.48–1.00; P=0.04). The comparison is difficult to interpret because the denominators differ: patients in the delayed arm who recovered without RRT contribute zero days, while those who deteriorated contribute prolonged courses. Neither dose nor modality influenced duration of support in any trial. Notably, an ancillary analysis of the ELVIS cohort identified prolonged duration of RRT as an independent predictor of severe long-term chronic kidney disease up to 12 months (odds ratio 1.03 per day, 95% CI 1.02–1.05), which supplies an additional rationale for keeping the total duration of extracorporeal support as short as is safely achievable.^{32,61}

Extracorporeal circuit (filter) life span

Table 14. Filter / circuit life span by anticoagulation strategy

Trial (year)	Comparison	Citrate arm	Heparin arm	Statistical result	Direction
Monchi (2004)	Citrate vs adjusted-dose UFH	70 h (IQR 44–140)	40 h (IQR 17–48)	P=0.0007	Favours citrate
Kutsogiannis (2005)	Regional citrate vs systemic heparin	124.5 h (95% CI 95.3–157.4)	38.3 h (95% CI 24.8–61.9)	P<0.001	Favours citrate
Oudemans-van Straaten (2009)	Citrate vs nadroparin	Similar circuit survival	Similar	Not significant	Neutral
Hetzel (2010)	Citrate vs UFH	Longer haemofilter patency	Shorter	Significant in favour of citrate	Favours citrate
Schilder (2014)	Citrate vs UFH	Median 46 h	32 h	P=0.02	Favours citrate
Stucker (2015)	Citrate vs heparin	49 ± 29 h	28 ± 23 h	P=0.004	Favours citrate
Gattas (2015)	Citrate–calcium vs heparin–protamine	39.2 h (95% CI 32.1–48.0)	22.8 h (95% CI 13.3–34.0)	Log-rank P=0.0037; HR for clotting 2.03 (1.36–3.03), P<0.0005	Favours citrate
Zarbock (RICH, 2020)	Citrate vs heparin	Median 47 h (IQR 19–70)	26 h (IQR 12–51)	Difference 15 h (95% CI 11–20); P<0.001	Favours citrate

This is the most reproducible statistically significant finding in the entire literature of extracorporeal renal support. In seven of eight randomized comparisons, regional citrate anticoagulation prolonged circuit life span significantly, and the magnitude of the effect is large: in the RICH trial, the largest and most rigorous of these, median filter life span was 47 hours with citrate versus 26 hours with heparin, a difference of 15 hours (95% CI 11 to 20; $P<0.001$). Gattas and colleagues, using repeated-events survival analysis across 857 circuits, found that patients receiving heparin–protamine were more than twice as likely to experience circuit clotting (hazard ratio 2.03, 95% CI 1.36–3.03; $P<0.0005$). Schilder and colleagues additionally showed that citrate reduced the number of filters consumed ($P=0.002$), reduced treatment down-time within the first 72 hours ($P=0.002$), and lowered the direct cost of therapy.^{22,23,29,30,37,53,54,55}

The clinical corollary is direct: with citrate, the prescribed dose is far more likely to be the delivered dose. Because delivered rather than prescribed clearance determines metabolic control, circuit longevity is not a technical nicety but the principal determinant of therapeutic adequacy in continuous renal replacement therapy.³⁷

3.4.10 Outcome 10 — Infectious complications

Table 15. Catheter-related bloodstream infection and new infection

Trial (year)	Comparison	Experimental	Comparator	Statistical result	Direction
Gaudry (AKIKI, 2016)	Early vs delayed initiation	10%	5%	$P=0.03$	Favours delayed
Zarbock (RICH, 2020)	Citrate vs heparin	68.0% (204/300)	55.4% (164/296)	Difference 12.6% (4.9–20.3); $P=0.002$	Favours heparin
STARRT-AKI (2020)	Accelerated vs standard	23.0% adverse events	16.5% (245/1489)	$P<0.001$	Favours standard

Trial (year)	Comparison	Experimental	Comparator	Statistical result	Direction
Naorungroj (pooled, 2021)		(346/1503)			
	Earlier vs later initiation	—	—	RR 0.50 (0.29–0.86) favouring later initiation	Favours later
Li (pooled, 2021)	Early vs delayed initiation	—	—	RR 1.34 (1.01–1.78); P=0.04 for RRT-associated infection	Favours delayed
Schilder (2014)	Citrate vs heparin	No excess infection	—	Not significant	Neutral

Catheter-related bloodstream infection occurred in 10% of patients allocated to early initiation in AKIKI compared with 5% of those allocated to delay (P=0.03) — a statistically significant doubling of risk that follows directly from the fact that half of the delayed arm never received a dialysis catheter. Two independent meta-analyses confirm the effect at the level of the pooled literature: a risk ratio of 0.50 (95% CI 0.29–0.86) for catheter-related bloodstream infection favouring later initiation, and a risk ratio of 1.34 (95% CI 1.01–1.78) for RRT-associated infectious events with early initiation. In STARRT-AKI, adverse events overall were significantly more frequent with acceleration (23.0% versus 16.5%; P<0.001).^{33,38,47,48}

The RICH trial delivered an unexpected and important counter-signal within the anticoagulation domain: new infections were significantly more frequent with regional citrate than with systemic heparin (68.0% versus 55.4%; difference 12.6%, 95% CI 4.9% to 20.3%; P=0.002). Citrate chelates ionized calcium and may thereby impair calcium-dependent leucocyte signalling, and the longer circuit life spans achieved with citrate also mean longer indwelling catheter and circuit exposure. Of 38 pre-specified secondary endpoints in that trial, 34 showed no difference, so this finding requires cautious interpretation with respect to multiplicity; nonetheless it should temper any assumption that citrate is uniformly superior.³⁷

Bleeding and transfusion requirement

Table 16. Bleeding complications and transfusion requirement

Trial (year)	Comparison	Citrate / experimental	Heparin / comparator	Statistical result	Direction
Monchi (2004)	Citrate vs UFH	0.2 RBC units/day (IQR 0.0–0.4)	1.0 (IQR 0.0–2.0)	P=0.0008	Favours citrate
Kutsogiannis (2005)	Citrate vs heparin	Lower haemorrhage risk	Reference	Adjusted RR 0.14 (0.02–0.96); P=0.05	Favours citrate
Oudemans-van Straaten (2009)	Citrate vs nadroparin	Bleeding in 6 patients; discontinuation in 2	Bleeding in 16; discontinuation in 20	P=0.08 for bleeding; P<0.001 for discontinuation	Favours citrate
Hetzel (2010)	Citrate vs UFH	Lower bleeding risk	Higher	Significant	Favours citrate
Gattas (2015)	Citrate–calcium vs heparin–protamine	2 adverse events	11 adverse events	P=0.011	Favours citrate
Zarbock (RICH, 2020)	Citrate vs heparin	5.1% (15/300)	16.9% (49/296)	Difference –11.8% (–16.8 to –6.8); P<0.001	Favours citrate
Schwenger (2012)	SLED vs CVVH	1,375 ± 2,573 mL transfused	1,976 ± 3,316 mL	P=0.02	Favours SLED

The bleeding advantage of regional citrate is as robust as its circuit-longevity advantage and is quantitatively substantial. In RICH, bleeding complications occurred in 5.1% of citrate-treated

patients versus 16.9% of heparin-treated patients (absolute difference -11.8% , 95% CI -16.8% to -6.8% ; $P<0.001$) — a number needed to treat of approximately eight to prevent one bleeding event. Kutsogiannis and colleagues reported an adjusted relative risk of haemorrhage of 0.14 (95% CI 0.02–0.96; $P=0.05$) with citrate, and Oudemans-van Straaten and colleagues found that the assigned anticoagulant had to be discontinued in 20 of 73 heparin-treated patients but only 2 of 66 citrate-treated patients ($P<0.001$). Independently of anticoagulation, sustained low-efficiency dialysis significantly reduced transfusion volume compared with continuous haemofiltration (1,375 versus 1,976 mL; $P=0.02$).^{22,24,30,37,54}

Metabolic and electrolyte complications

Table 17. Metabolic and electrolyte complications

Trial (year)	Comparison	Complication	Experimental	Comparator	Statistical result
Bellomo (RENAL, 2009)	40 vs 25 mL/kg/h	Hypophosphataemia	65%	54%	$P<0.001$
Lumlertgul (FST, 2018)	Early vs standard initiation	Hypophosphataemia	More frequent	Less frequent	$P=0.002$
Qi (pooled, 2025)	Early vs delayed CRRT	Hypophosphataemia	—	—	RR 3.35 (2.18–5.15); $P<0.00001$
Qi (pooled, 2025)	Early vs delayed CRRT	Thrombocytopenia	—	—	RR 1.53 (1.11–2.10); $P=0.009$
Palevsky	Intensive vs less-	Electrolyte	More frequent	Less	Significant

Trial (year)	Comparison	Complication	Experimental	Comparator	Statistical result
(ATN, 2008)	intensive	disturbance		frequent	
Oudemans-van Straaten (2009)	Citrate vs nadroparin	Metabolic alkalosis	Less	More	P=0.001
Oudemans-van Straaten (2009)	Citrate vs nadroparin	Plasma calcium	Lower	Higher	P<0.001
Hetzel (2010)	Citrate vs UFH	Hyper-/hypocalcaemia, bicarbonate need	More frequent	Less frequent	Significant
Park (2016)	80 vs 40 mL/kg/h	Electrolyte disturbance	No difference	No difference	Not significant
Xiao (pooled, 2019)	Early vs late initiation	Metabolic acidosis	Less frequent	More frequent	RR 0.65 (0.43–0.99); P=0.04

Excess clearance is not biologically neutral. In RENAL, hypophosphataemia occurred in 65% of patients receiving 40 mL/kg/h versus 54% receiving 25 mL/kg/h ($P<0.001$), and in the ATN study electrolyte disturbance was significantly more frequent with intensive therapy. A recent meta-analysis of twelve randomized trials found that early initiation of continuous therapy more than tripled the risk of hypophosphataemia (risk ratio 3.35, 95% CI 2.18–5.15; $P<0.00001$) and significantly increased thrombocytopenia (risk ratio 1.53, 95% CI 1.11–2.10; $P=0.009$). These are

not trivial laboratory abnormalities: phosphate is essential for diaphragmatic contractility and for adenosine triphosphate regeneration, which supplies the mechanistic link to the ventilation findings in Section 3.4.14.^{18,19,36,41,50}

Within the anticoagulation domain, citrate produces a characteristic and predictable metabolic signature — less metabolic alkalosis but lower plasma ionized calcium, a higher incidence of both hypocalcaemia and hypercalcaemia, and greater need for supplementary bicarbonate — all of which are manageable with protocolized monitoring but which mandate the availability of frequent ionized-calcium measurement before citrate can be adopted safely. Conversely, early initiation significantly reduced metabolic acidosis (risk ratio 0.65, 95% CI 0.43–0.99; $P=0.04$), the one metabolic outcome that favours the earlier strategy.^{22,23}

Haemodynamic instability and vasopressor requirement

Table 18. Haemodynamic tolerance

Trial (year)	Comparison	Finding	Statistical result	Direction
Palevsky (ATN, 2008)	Intensive vs less-intensive	Hypotension during intermittent dialysis occurred in more patients assigned to intensive therapy, although the proportion of sessions complicated by hypotension was similar	Significant by patient	Favours less intensive
Augustine (2004)	CVVHD vs IHD	Significant fall in mean arterial pressure during intermittent haemodialysis, not observed with continuous therapy; greater net volume removal over 72 h with	Significant for blood pressure; no survival benefit	Favours continuous (physiologically)

Trial (year)	Comparison	Finding	Statistical result	Direction
Vinsonneau (2006)		continuous therapy		
	CVVHDF vs IHD	With protocolized optimization (cooled dialysate, higher sodium, longer sessions), intermittent haemodialysis was tolerated in almost all patients with multiple-organ dysfunction	No survival difference	Neutral
Schwenger (2012)	SLED vs CVVH	Haemodynamic stability did not differ between hybrid and continuous therapy	Not significant	Neutral
Wald (OMAKI, 2012)	CVVH vs CVVHD	Trend to greater SOFA reduction over the first week with convective clearance, driven by lower vasopressor requirement (−0.8; 95% CI −2.1 to +0.5)	Not significant	Neutral
Atan (2018)	High cut-off vs standard CVVH	Median noradrenaline-free hours at day 7: 32 h vs 56 h	P=0.520	Neutral
Li (pooled, 2021)	Early vs delayed initiation	Hypotension	RR 1.42 (1.23–1.63); P<0.00001	Favours delayed
Xiao (pooled, 2019)	Early vs late initiation	Hypotension	RR 1.24 (1.08–1.43);	Favours delayed

Trial (year)	Comparison	Finding	Statistical result	Direction
Qi (pooled, 2025)			P=0.003	
	Early vs delayed CRRT	Hypotension	RR 1.26 (1.06–1.50); P=0.008	Favours delayed

Three independent meta-analyses converge on the same statistically significant conclusion: early initiation of renal replacement therapy significantly increases the incidence of hypotension, with pooled risk ratios of 1.42 (95% CI 1.23–1.63), 1.24 (95% CI 1.08–1.43) and 1.26 (95% CI 1.06–1.50). This is the most plausible single mechanism by which an earlier strategy could impair kidney recovery while leaving mortality unchanged, and it links Outcome 13 directly to Outcomes 5 and 6. ^{48,50}

The modality literature demonstrates that haemodynamic tolerance is a property of the prescription rather than of the machine. Continuous therapy is intrinsically gentler, and Augustine and colleagues documented a significant fall in mean arterial pressure during intermittent sessions that was absent during continuous therapy; yet when the Hemodiafe investigators applied a protocol of cooled dialysate, higher dialysate sodium and extended session duration, intermittent haemodialysis was successfully delivered to almost all patients with multiple-organ dysfunction syndrome without any survival disadvantage. Where continuous therapy is unavailable or unaffordable, an optimized intermittent prescription is an evidence-supported alternative rather than a compromise. ^{14,16}

Mechanical ventilation and organ-support burden

Table 19. Mechanical ventilation and organ-support outcomes

Trial (year)	Comparison	Experimental	Comparator	Statistical result	Direction
Sharma (ATN secondary,	Intensive vs less-intensive	2.07 ventilator-free	3.08 ventilator-	HR for successful extubation 0.67 (0.52–	Favours less

Trial (year)	Comparison	Experimental	Comparator	Statistical result	Direction
2020)		days	free days	0.88); P<0.001	intensive
Schwenger (2012)	SLED vs CVVH	17.7 ± 19.4 ventilator days	20.9 ± 19.8	P=0.047	Favours SLED
Schefold (CONVINT, 2014)	CVVH vs IHD	No difference in ventilator days	No difference	Not significant	Neutral
Gaudry (AKIKI post hoc, 2018)	Early vs delayed in ARDS	Time to successful extubation	No difference	P=0.43	Neutral
Chen (pooled, 2020)	Early vs late initiation	Fewer ventilation days with early strategy	—	Mean difference −3.98 days (−7.81 to −0.15)	Favours early
Rimbaud (AKIKI 2 secondary, 2024)	More-delayed vs delayed in coma	Time awake 7.63 days	10.11 days	HR for awakening 0.36 (0.17–0.78); P=0.010	Favours delayed
Zarbock (ELAIN, 2016)	Early vs delayed	No significant effect on organ dysfunction	—	Not significant	Neutral

The secondary analysis of the ATN study in 907 mechanically ventilated participants produced one of the most clinically arresting findings of the dose domain: patients randomized to more intensive renal replacement therapy had a 33.3% lower hazard rate of successful extubation

(hazard ratio 0.67, 95% CI 0.52–0.88; $P < 0.001$) and accrued fewer ventilator-free days over 14 days (2.07 versus 3.08; $P < 0.001$). The investigators proposed excessive phosphate loss as the mediating mechanism, which is entirely consistent with the significant excess of hypophosphataemia in RENAL and in the pooled early-initiation literature. Excess clearance therefore does not merely fail to help — it plausibly harms, through a defined and preventable metabolic pathway.^{19,41}

At the other extreme of the therapeutic window, the AKIKI 2 coma substudy showed that excessive postponement significantly impaired neurological recovery: the transition intensity from coma to awakening was reduced by nearly two thirds with the more-delayed strategy (hazard ratio 0.36, 95% CI 0.17–0.78; $P = 0.010$). Both too much and too late are demonstrably harmful; the therapeutic target is the middle.⁴⁵

Length of stay, nursing burden and cost

Table 20. Length of stay and resource utilization

Trial (year)	Comparison	ICU length of stay	Hospital length of stay	Resource / cost	Statistical result
Zarbock (ELAIN, 2016)	Early vs delayed	No significant effect	51 vs 82 days	—	HR 0.34 (0.22–0.52); $P < 0.001$ for hospital stay
Schwenger (2012)	SLED vs CVVH	19.6 ± 20.1 vs 23.7 ± 21.9 days	—	Substantially reduced nursing time and lower cost	$P = 0.04$ for ICU stay; $P < 0.001$ for nursing time
Schilder (2014)	Citrate vs heparin	—	—	Lower cost in the first 72 h of prescribed CVVH	Favours citrate
Lins (SHARF)	CRRT vs IRRT	No difference	No difference	—	Not significant

Trial (year)	Comparison	ICU length of stay	Hospital length of stay	Resource / cost	Statistical result
4, 2009)					
Uehlinger (2005)	CVVHDF vs IHD	—	20 vs 30 days (survivors)	—	P=0.25
Naorungroj (pooled, 2021)	Earlier vs later initiation	MD -1.18 days (-1.95 to -0.42)	MD -2.14 days (-4.13 to -0.14)	—	Both significant, favouring earlier
Qi (pooled, 2025)	Early vs delayed CRRT	MD -3.24 days (-5.14 to -1.35); P=0.0008	MD -7.00 days (-14.60 to 0.60); P=0.07	—	ICU stay significant

Two significant resource findings emerge. First, earlier initiation is associated with significantly shorter ICU stay in pooled analyses (mean difference -1.18 days, 95% CI -1.95 to -0.42, and -3.24 days, 95% CI -5.14 to -1.35 respectively), and ELAIN reported a strikingly shorter hospital stay with early initiation (51 versus 82 days; hazard ratio 0.34, 95% CI 0.22–0.52; $P<0.001$). These estimates must be interpreted with care, since shorter length of stay in a population with unchanged mortality can reflect either faster recovery or earlier death. Second, and more securely, sustained low-efficiency dialysis using a single-pass batch system significantly reduced ICU stay (19.6 versus 23.7 days; $P=0.04$), ventilator days ($P=0.047$), transfusion volume ($P=0.02$) and nursing time devoted to renal replacement therapy ($P<0.001$), yielding lower overall cost at equivalent 90-day mortality (49.6% versus 55.6%; $P=0.43$).^{24,32,47,50}

For institutions in resource-variable settings this is the single most economically actionable result in the review: a hybrid modality delivers outcomes indistinguishable from continuous therapy at materially lower cost in consumables and nursing time, while regional citrate reduces filter consumption and the cost of the first 72 hours of therapy.^{24,29}

Summary of statistically significant findings

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Table 21. All statistically significant results identified across the 29 included trials and their supporting analyses

Outcome	Comparison	Effect estimate (95% CI)	P value	Source	Interpretation
RRT dependence at day 90 in survivors	Accelerated vs standard initiation	RR 1.74 (1.24–2.43)	<0.05	STARRT-AKI (n=3,019)	Acceleration nearly doubles dialysis dependence
Adverse events	Accelerated vs standard initiation	23.0% vs 16.5%	<0.001	STARRT-AKI	Acceleration increases harm
Catheter-related bloodstream infection	Early vs delayed initiation	10% vs 5%	0.03	AKIKI (n=620)	Delay avoids catheter exposure
Catheter-related bloodstream infection (pooled)	Earlier vs later initiation	RR 0.50 (0.29–0.86)	<0.05	Naorungroj meta-analysis	Confirms trial-level finding
60-day mortality	More-delayed vs delayed initiation	Adjusted HR 1.65 (1.09–2.50)	0.018	AKIKI 2 (n=278)	Excessive postponement is harmful
Awakening from coma	More-delayed vs delayed initiation	HR 0.36 (0.17–0.78)	0.010	AKIKI 2 secondary (n=168)	Uraemia delays neurological recovery
Hypotension (pooled)	Early vs delayed initiation	RR 1.42 (1.23–1.63)	<0.00001	Li meta-analysis	Early therapy destabilizes haemodynamics

Outcome	Comparison	Effect estimate (95% CI)	P value	Source	Interpretation
Hypophosphataemia	40 vs 25 mL/kg/h	65% vs 54%	<0.001	RENAL (n=1,508)	Excess clearance depletes phosphate
Hypophosphataemia (pooled)	Early vs delayed CRRT	RR 3.35 (2.18–5.15)	<0.00001	Qi meta-analysis	Consistent and large effect
Time to successful extubation	Intensive vs less-intensive RRT	HR 0.67 (0.52–0.88)	<0.001	ATN secondary (n=907)	Intensive therapy prolongs ventilation
Filter life span	Citrate vs heparin	47 vs 26 h; difference 15 h (11–20)	<0.001	RICH (n=596)	Citrate markedly prolongs circuit life
Circuit clotting	Heparin–protamine vs citrate–calcium	HR 2.03 (1.36–3.03)	<0.0005	Gattas (857 circuits)	Confirms circuit advantage of citrate
Bleeding complications	Citrate vs heparin	5.1% vs 16.9%; difference –11.8% (–16.8 to –6.8)	<0.001	RICH	Citrate halves bleeding; NNT ≈ 8
New infections	Citrate vs heparin	68.0% vs 55.4%;	0.002	RICH	Counter-signal against citrate

Outcome	Comparison	Effect estimate (95% CI)	P value	Source	Interpretation
Ventilator days, ICU days, transfusion, nursing time		difference 12.6% (4.9–20.3)			
	SLED vs CVVH	17.7 vs 20.9 d; 19.6 vs 23.7 d; 1,375 vs 1,976 mL	0.047 / 0.04 / 0.02 / <0.001	Schwenger (n=232)	Hybrid modality is resource-sparing
	Early vs delayed initiation	HR 0.66 (0.45–0.97); OR 0.55 (0.32–0.93)	0.03 / 0.02	ELAIN (n=231)	Positive but not replicated in multicentre trials
Survival at 15 days after cessation	35/45 vs 20 mL/kg/h	57%/58% vs 41%	0.0007 / 0.0013	Ronco (n=425)	Not replicated; winner's curse
28- and 90-day survival	CVVHDF vs CVVH	59% vs 39%; 59% vs 34%; HR 0.59 (0.40–0.87)	0.03 / 0.0005	Saudan (n=206)	Not replicated in larger dose trials
Heterogeneity of treatment effect	Early vs delayed by AKI diagnostic criterion	Interaction P=0.021; creatinine-only 58% vs 42%	0.028	IDEAL-ICU substudy	Phenotype modifies the effect

CI = confidence interval; CRRT = continuous renal replacement therapy; HR = hazard ratio; NNT = number needed to treat; OR = odds ratio; RR = risk ratio; SLED = sustained low-efficiency dialysis. Green shading denotes a significant result whose direction supports the recommendations of this review; red shading denotes a significant result that opposes them.

Certainty of evidence (GRADE)

Table 22. GRADE Summary of Findings across the fifteen outcome domains

Outcome domain	Trials (participants)	Effect	Risk of bias	Inconsistency	Imprecision	Certainty
O1 Mortality 28–30 d	10 (2,900)	No difference (RR 1.01, 0.91–1.13)	Not serious	Not serious ($I^2=0\%$)	Not serious	HIGH
O2 Mortality 60 d	5 (1,864)	No difference; harm from excessive delay	Not serious	Not serious	Serious	MODERATE
O3 Mortality 90 d	11 (7,600)	No difference (RR 1.00, 0.93–1.09)	Not serious	Not serious	Not serious	HIGH
O4 ICU / in-hospital mortality	6 (1,507)	No difference after adjustment	Serious	Not serious	Serious	LOW

Outcome domain	Trials (participants)	Effect	Risk of bias	Inconsistency	Imprecision	Certainty
O5 Kidney recovery	10 (4,100)	Conflicting ; phenotype-dependent	Serious	Serious	Not serious	LOW
O6 RRT dependence in survivors	7 (5,600)	Increased with acceleration (RR 1.74, 1.24–2.43)	Not serious	Not serious	Not serious	HIGH
O7 Avoidance of RRT	7 (5,169)	38–49% avoid RRT under a delayed strategy	Not serious	Not serious	Not serious	HIGH
O8 Duration of RRT	7 (3,700)	No consistent difference	Serious	Serious	Serious	VERY LOW
O9 Filter life span	8 (1,900)	Citrate superior (+15 h, 11–20)	Not serious	Not serious	Not serious	HIGH
O10 Infectious complications	6 (5,200)	Increased with early	Not serious	Serious	Not serious	MODERATE

Outcome domain	Trials (participants)	Effect	Risk of bias	Inconsistency	Imprecision	Certainty
O11 Bleeding / transfusion		initiation; increased with citrate				
	7 (1,700)	Citrate superior (−11.8%, −16.8 to −6.8)	Not serious	Not serious	Not serious	HIGH
O12 Metabolic complications	10 (4,500)	Increased with higher dose and earlier start	Not serious	Not serious	Serious	MODERATE
O13 Haemodynamic instability	9 (4,000)	Increased with early initiation (RR 1.24–1.42)	Serious	Not serious	Not serious	MODERATE
O14 Mechanical ventilation	7 (2,600)	Prolonged by intensive RRT (HR 0.67, 0.52–0.88)	Not serious	Serious	Not serious	MODERATE

Outcome domain	Trials (participants)	Effect	Risk of bias	Inconsistency	Imprecision	Certainty
O15 Length of stay and cost	7 (2,000)	SLED resource-sparing; LOS estimates confounded	Serious	Serious	Serious	VERY LOW

GRADE certainty: HIGH = further research is very unlikely to change confidence in the estimate; MODERATE = further research is likely to have an important impact and may change the estimate; LOW = further research is very likely to have an important impact and is likely to change the estimate; VERY LOW = any estimate is very uncertain. Participant counts are approximate and reflect the trials contributing usable data to each domain.

Subgroup and sensitivity analyses

Pre-specified subgroup analyses generated three consistent signals. First, in surgical populations, syntheses have repeatedly reported a mortality benefit for earlier initiation (risk ratio 0.60, 95% CI 0.44–0.80 in one recent synthesis; risk ratio 0.78, 95% CI 0.64–0.96 in another), and the two positive timing trials — ELAIN and, in the cardiac-surgical literature, the pooled post-cardiac-surgery experience — both derive from surgical cohorts. This subgroup is characterized by a defined and timed insult, an inflammatory response of predictable trajectory, and a high prevalence of fluid overload, all of which plausibly favour earlier decongestive therapy. Second, in continuous-modality subgroups, accelerated initiation has been associated with lower mortality and a higher probability of eventual dialysis independence, whereas in non-continuous modality subgroups and in patients with SOFA scores above 11 accelerated initiation increased the risk of dialysis dependence. Third, in septic populations the benefit of earlier initiation disappears entirely: the AKIKI post hoc analysis found no influence of baseline sepsis status ($P=0.28$), ARDS status

($P=0.94$) or severity scores ($P=0.77$ and $P=0.46$) on the comparison of 60-day mortality, and IDEAL-ICU, conducted exclusively in septic shock, was stopped for futility.^{35,42,49}

Sensitivity analyses were reassuring in every direction. Excluding the two trials at high risk of bias did not alter any domain-level conclusion. Restricting the timing domain to the four multicentre trials at low risk of bias (AKIKI, IDEAL-ICU, STARRT-AKI, AKIKI 2; 4,405 participants) produced an unchanged null mortality result with narrower confidence limits. Excluding trials terminated early (IVOIRE, IDEAL-ICU, RICH) did not change the dose, timing or anticoagulation conclusions. Restricting the dose domain to the two trials with more than 1,000 participants (ATN and RENAL, 2,632 participants) produced odds ratios of 1.09 (95% CI 0.86–1.40) and 1.00 (95% CI 0.81–1.23) respectively, both firmly null. Trial sequential analysis performed by an independent group demonstrated that the cumulative Z-curve for the timing question has crossed the futility boundary and exceeded the required information size of 2,949 patients, meaning that the null result for mortality is definitive and that further trials of undifferentiated timing would be uninformative.^{18,19,48}

DISCUSSION

Principal findings

This systematic review of 29 randomized controlled trials enrolling 12,129 participants establishes five principal findings. First, and most consequentially, no renal replacement therapy strategy — not accelerated initiation, not higher-intensity clearance, not continuous modality, not regional citrate anticoagulation — reduces all-cause mortality in adults with severe acute kidney injury. The confidence intervals around the null are narrow, the largest trials are the most decisively null, and trial sequential analysis indicates that the required information size has been exceeded. Second, despite this, the randomized evidence is rich in statistically significant, clinically actionable non-fatal effects, nineteen of which are collated in Table 21. Third, a delayed strategy with strictly defined mandatory triggers spares 38–49% of eligible patients from ever receiving extracorporeal support, without any mortality penalty and with significant reductions in catheter-related bloodstream infection and haemodynamic instability. Fourth, that permissive strategy has a defined lower boundary: once oliguria has persisted beyond 72 hours or blood urea nitrogen exceeds 112

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mg/dL, further postponement significantly increases 60-day mortality and significantly impairs neurological recovery. Fifth, regional citrate anticoagulation is the superior circuit strategy on the two outcomes that matter most for delivered dose and patient safety — filter life span and bleeding — although it carries a significant excess of new infection that has not been adequately explained.
33,35,37,38,39,45,46,48

Interpretation of the null mortality result

The consistency of the mortality null across four independent prescriptive domains, three decades, five continents and four orders of magnitude of trial size is not a failure of the evidence base; it is a substantive biological finding. Mortality in severe acute kidney injury is determined by the severity and reversibility of the underlying critical illness — septic shock, multiple-organ dysfunction, cardiogenic collapse — and not by the manner in which the kidney's excretory function is temporarily substituted. Once a threshold of adequacy is reached, additional clearance, earlier clearance or a technically different form of clearance addresses a physiological deficit that is no longer rate-limiting for survival. The AKI-EPI observation that adjusted mortality rises steeply with AKI stage, coupled with the randomized demonstration that modifying the treatment of that stage changes nothing, indicates that severe AKI is principally a marker of illness severity rather than a modifiable mediator of death once renal support is instituted.^{1,38,46}

This interpretation is strengthened, not weakened, by the two eras of positive trials. Ronco and colleagues reported absolute survival differences of 16–17 percentage points between 20 and 35 mL/kg/h; nine years later, RENAL found precisely zero difference between 25 and 40 mL/kg/h in 1,508 patients. This is the archetypal winner's curse. To cross the conventional significance threshold, a trial with 90 patients per group requires an observed absolute difference of approximately 20 percentage points even when the true effect is zero; as sample size rises, the effect size required for significance converges on the truth. Effect-size shrinkage between a small discovery trial and a large replication trial is therefore an expected consequence of null-hypothesis significance testing and does not require any imputation of bias or misconduct. The appropriate epistemic response is not to reconcile the trials but to recognize that the larger trial estimates the population effect and the smaller one does not.^{12,19,58}

Timing: from a binary question to a bounded window

The timing literature has passed through three phases. In the first, observational syntheses reported dramatic benefits from earlier initiation — an odds ratio for 28-day mortality of 0.45 (95% CI 0.28–0.72) in one influential meta-analysis of 15 mostly non-randomized studies — driven by confounding by indication, since patients who survive long enough to be dialysed late are systematically different from those dialysed early. In the second phase, adequately powered randomized trials dismantled that conclusion: AKIKI (n=620), IDEAL-ICU (n=488) and STARRT-AKI (n=3,019) each found no mortality difference, and the individual-patient-data meta-analysis of nine trials (1,879 patients with severe AKI) found a risk ratio of 1.01 (95% CI 0.91–1.13) with I^2 of exactly 0%. In the third and current phase, AKIKI 2 has established that the permissive strategy is not unlimited, and secondary analyses have established that the effect is heterogeneous across phenotypes.^{33,35,38,39,46,51}

The clinical question is therefore no longer "early or late?" but "how do I keep this patient inside the therapeutic window?". The upper boundary is set by the mandatory indications — refractory hyperkalaemia, severe metabolic acidosis, diuretic-resistant pulmonary oedema and overt uraemic complications — which mandate immediate initiation and were exclusion criteria in every timing trial, so that the randomized evidence has never questioned them and does not do so here. The lower boundary is set by AKIKI 2: oliguria beyond 72 hours or blood urea nitrogen above 112 mg/dL. Between those boundaries, watchful waiting with intensive monitoring is the evidence-based default.^{33,39}

Three phenotype-modifying observations refine this further and are of direct bedside relevance. The IDEAL-ICU substudy showed a significant interaction between the diagnostic criterion for AKI and the effect of initiation timing (adjusted interaction $P=0.021$), with significant harm from early initiation in patients diagnosed by creatinine elevation alone (58% versus 42% mortality; $P=0.028$). The pooled AKIKI/IDEAL-ICU personalization analysis showed significant heterogeneity of treatment effect ($P=0.023$), with benefit from an early strategy confined to patients at intermediate-to-high predicted risk of needing RRT within 48 hours (absolute risk difference –14%, 95% CI –27% to –1%). And subgroup syntheses show a consistent survival benefit for

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earlier initiation in surgical but not medical or septic populations. Together these findings suggest that the null result of the main trials is an average of opposing effects in distinguishable subgroups, which is precisely the situation in which enrichment-based trial design becomes mandatory.^{43,44,49}

Dose: the primacy of delivered over prescribed clearance

The dose domain is now closed for practical purposes. ATN and RENAL together randomized 2,632 patients and found no difference in mortality, kidney recovery, non-renal organ failure or duration of support. Escalation into the high-volume range in sepsis — 50 versus 85 mL/kg/h, 35 versus 70 mL/kg/h, 40 versus 80 mL/kg/h — produced no benefit in any of three trials, even where cytokine removal was demonstrably and significantly achieved. The prevailing recommendation of a delivered effluent dose of 20–25 mL/kg/h for continuous therapy, or thrice-weekly intermittent haemodialysis with a per-treatment Kt/V of 1.2–1.4, is directly supported by the comparator arms of these trials.^{15,18,19,25,34}

Two operational corollaries deserve emphasis. First, prescribed dose and delivered dose diverge substantially in practice because of circuit down-time, clotting and procedural interruptions; this is why the circuit-longevity advantage of citrate (Section 4.6) has greater practical importance than any incremental increase in the prescription. Second, higher intensity is not merely futile but demonstrably harmful along a defined metabolic pathway: significant excess hypophosphataemia in RENAL (65% versus 54%; $P < 0.001$), significant excess electrolyte disturbance and intradialytic hypotension in ATN, and a significant 33% reduction in the hazard of successful extubation in the ATN ventilation analysis. Phosphate depletion impairs diaphragmatic contractility and adenosine triphosphate regeneration; the mechanistic chain from over-clearance to prolonged ventilation is therefore both plausible and preventable by protocolized phosphate repletion or phosphate-containing replacement solutions.^{18,19,41}

Modality: equivalence, and its implications for resource-variable practice

Seven randomized comparisons of continuous, intermittent and hybrid modalities, enrolling 1,531 patients, are unanimous: modality does not determine survival. The one trial appearing to show a difference was undermined by baseline imbalance that reversed the finding on adjustment. The Hemodiafe trial demonstrated that when the intermittent prescription is optimized — cooled

dialysate, higher dialysate sodium, extended session duration, identical membrane and buffer — intermittent haemodialysis can be delivered to almost all patients with multiple-organ dysfunction syndrome at equivalent survival. Sustained low-efficiency dialysis using a single-pass batch system produced equivalent 90-day mortality while significantly reducing ventilator days, ICU days, transfusion volume and nursing time.^{11,16,24,28}

For Indonesian and comparable practice environments this evidence is emancipatory rather than merely permissive. Continuous renal replacement therapy is expensive in consumables, requires continuous specialized nursing, and is unavailable in many secondary-level intensive care units. The randomized evidence states unambiguously that its absence does not condemn a patient to a worse outcome, provided the alternative is delivered with attention to haemodynamic tolerance. Modality should therefore be selected on the basis of haemodynamic stability, the need for controlled fluid removal, staffing, and cost — not on the belief that one modality saves lives. Where haemodynamic instability is severe, continuous or hybrid therapy remains physiologically preferable; where it is not, intermittent therapy is fully adequate.^{16,20,24,28}

Anticoagulation: the domain with the strongest positive evidence

Anticoagulation is the one domain in which a strategy is unequivocally and reproducibly superior on patient-important outcomes. Across eight randomized comparisons, regional citrate prolonged filter life span in seven, with the largest and most rigorous trial reporting a median of 47 versus 26 hours (difference 15 hours, 95% CI 11 to 20; $P < 0.001$), and reduced bleeding complications from 16.9% to 5.1% (absolute difference -11.8% , 95% CI -16.8% to -6.8% ; $P < 0.001$), a number needed to treat of approximately eight. Citrate also reduced the number of filters consumed, reduced circuit down-time, reduced transfusion requirement, and lowered direct cost. The mortality co-primary endpoint of the RICH trial did not reach significance (adjusted hazard ratio 0.79, 95% CI 0.63–1.004; $P = 0.054$), but the trial was terminated early and underpowered for that endpoint, and the point estimate is directionally favourable.^{29,30,37,53,54,55}

Two cautions must accompany this recommendation. The significant excess of new infections with citrate in the RICH trial (68.0% versus 55.4%; $P = 0.002$) emerged among 38 pre-specified secondary endpoints of which 34 were null, so multiplicity is a legitimate concern;

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nevertheless, a mechanism exists in the chelation of ionized calcium and consequent impairment of calcium-dependent leucocyte function, and the finding should not be dismissed. Second, citrate imposes a monitoring burden: it produces predictable hypocalcaemia, occasional hypercalcaemia, altered acid–base status and, in patients with severe hepatic dysfunction or shock-related impairment of citrate metabolism, the risk of citrate accumulation. Randomized data in patients with liver failure show that citrate remains superior to no anticoagulation for filter survival but at the cost of significantly more hypocalcaemia and elevated total-to-ionized calcium ratios. Regional citrate should therefore be the default only where frequent ionized-calcium measurement and a protocolized management algorithm are available.^{22,23,37}

Reconciling this synthesis with earlier and contemporaneous reviews

Our conclusions align closely with the individual-patient-data meta-analysis of nine timing trials, with the trial-sequential analysis of eleven trials that showed the futility boundary crossed, and with the pooled analysis showing shorter ICU and hospital stay but greater catheter-related infection and less RRT use with the respective strategies. They diverge from older observational syntheses reporting large mortality benefits from earlier initiation, and from a recent synthesis of 26 heterogeneous studies reporting a 19% relative reduction in 28-day mortality with early RRT (risk ratio 0.81, 95% CI 0.72–0.91) with substantial heterogeneity ($I^2 = 73\%$). That divergence is explained by design: syntheses that admit observational studies inherit confounding by indication, and heterogeneity at that level indicates that the pooled estimate is describing a mixture of populations rather than a single treatment effect. When the analysis is restricted to randomized evidence, heterogeneity falls to zero and the effect disappears.^{46,48,51,52}

Our synthesis extends previous work in three respects. It is the first to apply a single appraisal framework across all four prescriptive domains, which permits the observation — invisible in domain-restricted reviews — that the pattern of null mortality with significant non-fatal effects is identical in each domain. It incorporates the secondary and post hoc analyses of the landmark trials as a systematic evidence layer rather than as incidental citations, which yields the phenotype-modification findings that are among the most clinically important results reported here. And it organizes conclusions around a bounded therapeutic window rather than a binary early-

versus-late dichotomy, which is a more faithful representation of what the randomized evidence actually shows.^{42,43,44,45}

Clinical implications

The following algorithm follows directly from the graded evidence presented above and is offered for adaptation to local protocol.

- Initiate renal replacement therapy immediately, without deliberation, in the presence of any mandatory indication: refractory hyperkalaemia, severe metabolic acidosis unresponsive to medical therapy, diuretic-resistant pulmonary oedema, or overt uraemic complications including encephalopathy, pericarditis or bleeding diathesis. These indications were exclusion criteria in every timing trial and are therefore untouched by the null results reported here. (Certainty: not directly tested; universally accepted.)
- In the absence of a mandatory indication, adopt watchful waiting with intensive monitoring — hourly urine output, at least twice-daily biochemistry, and continuous reassessment of volume status. Between 38% and 49% of such patients will recover without ever requiring extracorporeal support. (Certainty: HIGH.)
- Do not extend watchful waiting beyond oliguria of 72 hours or a blood urea nitrogen concentration of 112 mg/dL (approximately 40 mmol/L urea). Beyond that point the hazard of death rises significantly (adjusted hazard ratio 1.65, 95% CI 1.09–2.50) and neurological recovery is significantly impaired. (Certainty: MODERATE.)
- Consider earlier initiation in patients with a defined and timed surgical insult, established fluid overload, and an intermediate-to-high predicted probability of requiring RRT within 48 hours. Do not apply this exception to patients with septic shock diagnosed by creatinine elevation alone, in whom early initiation was significantly harmful. (Certainty: LOW; hypothesis-generating.)
- Prescribe a delivered effluent dose of 20–25 mL/kg/h for continuous therapy, or thrice-weekly intermittent haemodialysis targeting a per-treatment Kt/V of 1.2–1.4. Audit delivered rather than prescribed dose. Do not escalate the prescription in sepsis. (Certainty: HIGH.)

- Select modality on haemodynamics, the need for controlled ultrafiltration, staffing and cost — not on any expectation of a survival difference. Sustained low-efficiency dialysis is a fully evidence-supported hybrid that is resource-sparing. (Certainty: HIGH for equivalence.)
- Use regional citrate as the default anticoagulant for continuous therapy wherever ionized-calcium monitoring and a management protocol exist, on the basis of significantly longer filter life span and significantly less bleeding. Use systemic heparin where citrate cannot be monitored safely, and reassess citrate in patients with severe hepatic dysfunction. (Certainty: HIGH.)
- Monitor and replace phosphate systematically in every patient receiving continuous therapy, particularly at higher effluent doses, given the significant excess of hypophosphataemia and its mechanistic link to prolonged mechanical ventilation. (Certainty: MODERATE.)
- Discontinue renal replacement therapy at the earliest safe opportunity: prolonged duration of RRT is an independent predictor of severe long-term chronic kidney disease (odds ratio 1.03 per day, 95% CI 1.02–1.05). (Certainty: LOW.)
- Arrange structured nephrological follow-up for all survivors. Around 5% require maintenance dialysis at four years, but more than 40% carry persistent albuminuria, and AKI is independently associated with incident and progressive chronic kidney disease, heart failure and death. (Certainty: MODERATE.)

Strengths of this review

- Comprehensive scope: this is the first synthesis to appraise all four RRT prescriptive domains within a single randomized-evidence framework, permitting cross-domain inference that domain-restricted reviews cannot generate.
- Methodological rigour: PRISMA 2020-compliant conduct and reporting, duplicate independent screening, extraction and RoB 2 appraisal, and GRADE rating of all fifteen pre-specified outcome domains.

- Analytical honesty: a pre-specified decision not to pool clinically non-substitutable comparisons, and citation of the published individual-patient-data meta-analysis as the quantitative anchor for the timing domain rather than an inferior aggregate-data recomputation.
- Outcome breadth: fifteen outcome domains, extending far beyond the mortality endpoint that has dominated and, arguably, distorted this literature.
- Systematic incorporation of secondary and post hoc analyses of the landmark trials, which yielded the phenotype-modification findings that constitute the most promising direction for future research.
- Explicit orientation towards resource-variable practice, with quantification of the cost, nursing and consumable implications of modality and anticoagulation choice.

Implications for future research

Four priorities emerge. First, further undifferentiated trials of RRT timing in unselected populations should not be undertaken: the required information size has been exceeded and the futility boundary crossed, so such trials would consume resources without generating information. Second, future trials should be enrichment-based, selecting patients by biomarker (NGAL, C-C motif chemokine ligand 14, the tissue inhibitor of metalloproteinases-2 and insulin-like growth factor-binding protein 7 combination), by furosemide stress test response, by AKI diagnostic phenotype, or by predicted probability of requiring RRT — the strategy already shown feasible by the FST trial and supported by the significant treatment-effect heterogeneity demonstrated in the AKIKI/IDEAL-ICU personalization analysis. Third, primary endpoints should move from all-cause mortality, which is demonstrably unmoved, to major adverse kidney events at 90 days, dialysis-free survival, kidney recovery trajectory and patient-reported functional outcomes. Fourth, pragmatic randomized trials of modality and anticoagulation are needed in low- and middle-income settings, where the relevant comparison is not continuous versus intermittent therapy but adequate versus inadequate delivery of whatever therapy is available.^{36,43,44,50,60}

CONCLUSION AND RECOMMENDATIONS

Conclusion

In adults with severe acute kidney injury, the randomized evidence assembled from 29 trials and 12,129 participants demonstrates that no renal replacement therapy strategy improves survival. Accelerated initiation does not reduce 90-day mortality (43.9% versus 43.7%; relative risk 1.00, 95% CI 0.93–1.09), higher-intensity clearance does not reduce 90-day mortality (44.7% in both arms; odds ratio 1.00, 95% CI 0.81–1.23), continuous modality does not outperform intermittent or hybrid therapy in any adequately adjusted analysis, and regional citrate does not significantly alter mortality. The null hypothesis regarding survival is therefore not rejected.

The alternative hypothesis is, however, decisively supported for non-fatal outcomes. A delayed strategy with strictly defined triggers spares 38–49% of eligible patients from extracorporeal therapy altogether while significantly reducing catheter-related bloodstream infection (10% versus 5%; $P=0.03$) and hypotension (pooled risk ratio 1.24–1.42). Accelerated initiation significantly increases dialysis dependence among 90-day survivors (relative risk 1.74, 95% CI 1.24–2.43) and adverse events (23.0% versus 16.5%; $P<0.001$). Excessive postponement is significantly harmful (adjusted hazard ratio for 60-day death 1.65, 95% CI 1.09–2.50). Higher-intensity clearance significantly increases hypophosphataemia (65% versus 54%; $P<0.001$) and significantly prolongs mechanical ventilation (hazard ratio for extubation 0.67, 95% CI 0.52–0.88). Regional citrate significantly prolongs filter life span (47 versus 26 hours; $P<0.001$) and significantly reduces bleeding (5.1% versus 16.9%; $P<0.001$), at the cost of significantly more new infection (68.0% versus 55.4%; $P=0.002$). Sustained low-efficiency dialysis significantly reduces ventilator days, ICU days, transfusion volume and nursing cost at equivalent survival.

The clinical meaning of this pattern is that the therapeutic target in severe acute kidney injury is not survival, which is governed by the underlying illness, but the avoidance of unnecessary therapy and of iatrogenic harm. The evidence-based standard is accordingly: watchful waiting within a bounded window, a modest and reliably delivered dose, a modality chosen for haemodynamics and resources rather than for any presumed survival advantage, and regional citrate as the default anticoagulant wherever it can be monitored safely.

Recommendations

For clinical practice

- Initiate renal replacement therapy immediately for any mandatory indication; otherwise adopt watchful waiting with intensive monitoring.
- Do not postpone initiation beyond 72 hours of oliguria or a blood urea nitrogen concentration of 112 mg/dL.
- Prescribe and audit a delivered continuous effluent dose of 20–25 mL/kg/h, or thrice-weekly intermittent haemodialysis with a per-treatment Kt/V of 1.2–1.4; do not escalate in sepsis.
- Choose modality on the basis of haemodynamic stability, ultrafiltration requirement, staffing and cost; optimize the intermittent prescription where continuous therapy is unavailable.
- Adopt regional citrate as the default anticoagulant where ionized-calcium monitoring and a protocol exist; retain heparin where they do not.
- Institute systematic phosphate monitoring and replacement in all patients on continuous therapy.
- Liberate patients from renal replacement therapy at the earliest safe opportunity and arrange structured nephrological follow-up for every survivor.

For institutions and health systems

- Develop and audit a written institutional protocol specifying mandatory initiation triggers, the permissible limits of watchful waiting, the target delivered dose, modality selection criteria and the anticoagulation algorithm.
- Where budgetary constraints preclude universal continuous therapy, invest in hybrid sustained low-efficiency dialysis capacity and in optimized intermittent prescriptions, which the randomized evidence shows to be non-inferior in survival and superior in resource utilization.
- Establish point-of-care ionized-calcium capability as a prerequisite for a citrate programme, and audit filter life span as a quality indicator of delivered dose.

- Create an AKI survivorship pathway with scheduled measurement of estimated glomerular filtration rate and albuminuria, given that more than 40% of survivors carry persistent proteinuria.

For research

- Cease further undifferentiated randomized trials of timing in unselected populations; the required information size has been exceeded and the futility boundary crossed.
- Design enrichment-based trials using damage biomarkers, functional stress testing or predicted-risk stratification, informed by the significant treatment-effect heterogeneity already demonstrated.
- Adopt major adverse kidney events at 90 days, dialysis-free survival and patient-reported functional outcomes as primary endpoints in place of all-cause mortality.
- Conduct pragmatic randomized trials of modality, anticoagulation and delivered-dose assurance in low- and middle-income settings, including a contemporary evaluation of acute peritoneal dialysis where extracorporeal therapy is unavailable.

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