Delayed versus Early Initiation of Renal Replacement Therapy for Severe Acute Kidney Injury: A Systematic Review and Individual Patient Data Meta-Analysis of Randomised Clinical Trials

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Summary

Background

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

Methods

In this systematic review and individual-patient data (IPD) meta-analysis, we searched MEDLINE via PubMed, EMBASE and the Cochrane Central Register of Controlled Trials for randomised trials published from April 2008 to December 2019 comparing delayed and early RRT initiation strategies in critically-ill patients with severe AKI. We contacted the principal investigator of each eligible trial to request IPD. The primary outcome was 28-day all-cause mortality.

Findings

Of 1031 studies identified, 10 were eligible. We obtained IPD for 9/10 trials (2083/2143 patients). Among patients with severe AKI (n=1879), there were 946 [50·3%] in the delayed strategy and 933 [49·6%] in the early strategy. Mortality at 28-days did not statistically significantly differ (366/837 [43·7%] in the delayed strategy vs 355/827[42·9%] in the early strategy; risk ratio 1·01 [95%CI, 0·91-1·13], p=0·80) with no heterogeneity across studies (I^2=0%; τ^2=0). Mortality did not statistically significantly differ at day-60, day-90 or at hospital discharge. Among patients allocated to the delayed strategy 390/929 (42%) did not receive RRT. There was no statistically significant difference between groups for other secondary outcomes including RRT free-days and complication rates.

Interpretation

RRT initiation strategy did not affect survival in critically ill patients with severe AKI who had no urgent indications for RRT. Delaying RRT initiation with close patient monitoring led to a reduced use of RRT which may allow for resource saving.

PROSPERO registration number: CRD42019125025

Funding source: No funding source.

Introduction

Acute kidney injury (AKI) occurs in up to 50% of critically ill patients and is associated with high morbidity and mortality [1–5]. Renal replacement therapy (RRT) will enable for a rapid correction of life-threatening complications associated by AKI such as severe hyperkalemia, profound metabolic acidosis, and severe pulmonary oedema due to fluid overload. However, the appropriate circumstances for initiating RRT when severe complications are not present remain controversial and uncertain [6]. Early initiation can allow better control of metabolic abnormalities and other complications associated with an increased mortality, but may needlessly expose patients to significant iatrogenic complications (hypotension, bleeding, infection, hypothermia) [7]. The deliberate deferral of RRT initiation may give time for spontaneous renal function recovery therefore obviating the need to ever commence RRT. Until recently, data from observational studies and small randomised controlled trials, have generated discordant conclusions [8,9,10]. Observational studies compared patients who all received RRT whether early or late. Therefore, they excluded patients who recovered from severe AKI without ever receiving RRT. This constitutes a major bias since such patients may have an excellent prognosis [11,12]. Methodological rigor mandates the conduct of a randomised clinical trial (RCT) comparing early RRT initiation with a delayed strategy [13] in which RRT is initiated only when pre-specified criteria are met [13]. Several such RCTs were conducted during the last decade. Whether these recent trials had adequate statistical power to detect a clinically important reduction in mortality with either strategy is a matter of ongoing debate. We therefore conducted a systematic review and individual patient data (IPD) meta-analysis to compare the effects of delayed versus early RRT initiation strategies on 28-day survival in a large population of critically-ill adult patients with severe AKI.

Methods

This systematic review with IPD meta-analysis was registered on PROSPERO (CRD42019125025, date of registration 03/12/2019) and followed a prespecified analysis plan. This article is reported using the Preferred Reporting Items for a Review and Meta-analysis of Individual Participant Data (PRISMA-IPD) [14].

Eligibility criteria

Eligible trials had to include adult (≧18 years) critically ill patients with severe AKI (defined by KDIGO AKI stage 2 or 3 [15]) and to compare the effect of two RRT initiation strategies (delayed versus early) on mortality. We included RCTs published in the last 10 years only because continuous progress in critical care quality resulted in considerable improvement in the prognosis of sepsis and/or multi-organ failure which are often associated with severe AKI [16,17]. There was no language restriction.

Search strategy and selection process

We conducted an electronic search from April 2008 to December 20 2019 of the following databases: MEDLINE via PubMed, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) using key-words and free-text words related to AKI, renal replacement therapy, intensive care unit as well as the sensitive filter developed by Cochrane to identify randomised controlled trials. The search algorithm for PubMed is reported in the supplementary material. We searched ClinicalTrials.gov and the international Clinical Trial registry platform (ICTRP) for completed and ongoing trials. We also hand-searched conference proceedings of the American Thoracic Society, the Society of Critical Care Medicine, the European Society of Intensive Care Medicine and the International Symposium on Intensive Care and Emergency Medicine for the last 5 years. Finally, we checked reference

lists of identified articles, recent editorials, and related reviews and contacted experts for further eligible trials.

Two investigators (NB and KC) independently screened the titles and abstracts for the eligibility criteria, to identify articles to be evaluated in full text. Definite article selection was only achieved after examination of the full text. Disagreement between the 2 reviewers was resolved by consensus. In case of persistent disagreement, arbitration by a third reviewer (SG) settled the discrepancy.

Data collection and risk of bias assessment

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

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

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

Outcomes

The primary outcome was 28-day all-cause mortality. Secondary outcomes were: time to death up to day 28, 60-day all-cause mortality, 90-day all-cause mortality, hospital mortality, duration of hospital stay, RRT-free days within day 28, number of patients who did not receive RRT with the delayed strategy, RRT dependence at hospital discharge, serum creatinine level at hospital discharge in the patients who were independent from RRT, mechanical ventilation-free days within day 28, vasopressor-free days within day 28, rate of adverse events potentially related to AKI or to RRT: hyperkalemia (> 6.5 mmol/l), severe cardiac rhythm disorders (ventricular tachycardia, ventricular fibrillation, torsades de pointes, third-degree atrioventricular block, or extreme bradycardia requiring medical treatment), severe bleeding events (bleeding requiring transfusion of at least one packed red blood cells or surgical control, or any intracranial bleeding).

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

Data analysis

We performed the statistical analysis for each outcome of interest using IPD. Intent-to-treat analysis was used for all outcomes. Treatment effects were expressed as risk ratios for binary outcomes, hazard ratios for time-to-event outcomes and mean difference for quantitative outcomes. The analysis involved both one-step and two-step methods for the primary outcome and two-step method for secondary outcomes. In the one-step method, we used a

generalized linear mixed effect model to analyse all trials simultaneously accounting for the clustering of data within each trial with a random effect. In the two-step method, we first analysed separately each trial using IPD before combining them using a random effects meta-analysis model to account for variability between trials. Heterogeneity was evaluated with the chi-square test, I^2 and between-study variance, τ^2. To explore heterogeneity, we performed subgroup analyses based on baseline characteristics (age, sex, sepsis, chronic kidney disease and Sequential Organ Failure Assessment [SOFA] score [19]) . For quantitative characteristics, we used the median value to define the subgroups. We performed interaction tests to evaluate whether intervention effect varied between subgroups.

We planned to conduct sensitivity analyses for the primary outcome analysis to account for risk of bias (exclusion of trials at high or unclear risk of bias for each domain) and for one study for which IPD were not obtained [20]. To do this latter analysis, we extracted the number of events and number of patients analysed in each group for 28-day mortality from the article. We also conducted sensitivity analyses to account for baseline prognostic factors (age, sex, sepsis, chronic kidney disease and SOFA), the few missing data on the primary outcome with multiple imputation and worst/best case scenario. Small study effect was evaluated with funnel plot.

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

Grading of the evidence

The quality of evidence for the 7 most important outcomes was graded with GRADEpro GDT (GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University, 2015 (developed by Evidence Prime, Inc. Available from [11,19–26]).

Role of the funding source

There was no funding source for this study

Results

Of 1031 studies identified, 261 were duplicates and 770 were screened for eligibility. One study published in 2009 was identified but was considered non-eligible because the period of patient inclusion was too old (1997-1999) [21]. After full-text review, 10 trials [20,22–30] (corresponding to 2143 participants) were deemed eligible (Figure 1). Five studies were performed in Europe, four in Asia, and one in North America. Individual patient data were obtained from 9 RCTs [22–30] (corresponding to 2083 patients). We could not obtain data for the 60 patients enrolled in one RCT [20]. This study was included in a sensitivity analysis (supplementary appendix).

Trial characteristics, population of patients and definitions used for early and delayed RRT strategies are provided in Table 1. The risk of bias in each study is presented in the supplementary appendix (eFigure 1). Most studies were at low risk of bias. There was no blinding for any subjective assessment.

In seven trials [22–28], all included patients had severe AKI (according to inclusion criteria, i.e. KDIGO AKI stage 2 or 3). In the two other trials (HEROICS [29] and HYPERDIA [30]), patients were included and randomised irrespective of presence of AKI. For these two trials, we selected only patients with severe AKI as attested by KDIGO AKI stage 2 or 3 in HYPERDIA or with renal SOFA score > or = 3 for HEROICS (because KDIGO stage was not available in that study), resulting in the inclusion of 33 patients (out of 35) from HYPERDIA and 42 patients (out of 224) from HEROICS in the IPD meta-analysis. Among 60 patients included in the trial by Srisawat et al, only 40 were randomised and therefore included in the IPD meta-analysis.

Finally, 1879 patients (946 [50·3%] who were allocated to a delayed strategy group and 933 [49·6%] who were allocated to early RRT) were included in the IPD meta-analysis. Baseline characteristics are presented in Table 2.

The prespecified primary outcome (28-day mortality) was not available in the trial by Jamale et al [28] which assessed mortality at hospital discharge only. In the 8 other studies, 28-day mortality was unavailable for seven patients (four in the early group and three in the delayed group). There were 366 deaths among 837 patients allocated to delayed RRT initiation group (43·7%) and 355 deaths among 827 patients allocated to early RRT initiation group (42·9%) within 28 days (risk ratio [RR] 1·01 [95%CI, 0·91-1·13], p=0·80) (Figure 2A). This corresponded to an overall risk difference of 0·01 (95%CI, -0·04-0·06). There was no evidence of heterogeneity across trials (I^2=0%, τ^2=0) (Figure 2A). All sensitivity analyses confirmed these results (eFigures 2, 3 and 4). The funnel plot did not show any major asymmetry (supplementary appendix, eFigure 5). Figure 2B shows the results of subgroup analyses for the primary outcome. There was no statistically significant interaction between baseline characteristics and treatment effect. Figure 3 shows the Kaplan-Meier estimate of the overall mortality up to day 28. The combined hazard ratio was 1·01 (95% CI, 0·87-1·17) with no evidence of heterogeneity across trials (I^2=0%, τ^2=0).

Among the 929 patients allocated to the delayed-strategy group, 390 (42·0%) never received RRT. However, RRT free-days through day 28 did not statistically significantly differ between groups (13·1 [SD 12·5] in the delayed group versus 12·0 [SD 11·7] in the early group, mean difference 1·0 (95% CI, -0·3-2·2], p=0·121). Mortality at days 60 and 90, hospital mortality, duration of hospital stay, RRT dependence at hospital discharge, serum creatinine level at hospital discharge (among patients with no RRT dependence at discharge), mechanical ventilation-free days through day 28, vasopressor-free days through day 28, and rate of adverse events did not statistically significantly differ between groups (Table 3 and 4).

The summary showing the quality of evidence is provided in the supplementary appendix (eTable 1). The quality of evidence was high for the following outcomes: 28-day mortality, 60-day mortality, hospital mortality and RRT free days through day 28.

Discussion

In this IDPMA, we found that mortality at Day 28 and beyond did not statistically significantly differ according to the timing of RRT initiation. Indeed, a strategy of early RRT initiation did not confer any tangible clinical benefits for patients. These results were robust in all sensitivity analyses and also when analysing 28-day mortality as a censored variable. These findings help inform one of the most controversial issues in critical care nephrology.

For years, most knowledge on the relationship between RRT timing and clinical outcomes came from observational studies and meta-analyses comprising these studies. These studies suggested a benefit of early RRT but were likely biased as they only included patients who actually received RRT. Patients with severe AKI who recovered kidney function without ever receiving RRT and who may have otherwise had an excellent prognosis were generally not considered [11,12].The release of larger RCTs in recent years significantly expanded the evidence base but yielded discrepant results [12,23,24]. Though there have been meta-analyses that included patients enrolled in these trials, this is the first conducted using individual patient-level data. In addition, most previous meta-analyses [8,31–33] did not include the most recent studies and all even included older trials that may no longer be relevant in the context of critical care [8,31–34].

We chose to restrict our meta-analysis to trials involving patients treated in the last ten years to reflect only those exposed to contemporary care. Indeed, continuous improvement of the outcome of critically-ill patients [16,17] undoubtedly impacted the prognosis of patients with severe AKI. Other organ failures and/or sepsis are frequently associated conditions in such patients. For instance, mortality of acute respiratory distress syndrome and of septic shock decreased by 9 and 25% respectively during recent years [16,17].

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

To be relevant, IPD meta-analyses need to include IPD for most eligible studies identified with a systematic review, which was the case in our study. We choose to include the *Jamale* trial despite the fact that this study was not strictly restricted to critical care units. However, study population had severe AKI and 80·2% had nevertheless at least one non-renal organ dysfunction. We obtained data for 9/10 eligible studies representing 97 % of all eligible patients. Only one small study with a higher risk of bias did not provide IPD [20] but our results were consistent when accounting for this study in a sensitivity analysis.

Our IPD meta-analysis involved more than 1800 patients (among them 1664 were included in the analysis of the primary outcome). This large population encompasses the variety of disorders encountered in critically ill patients as it was composed of mixed (medical and surgical) patients with many different admission diagnosis and organ failures.

By definition a delayed strategy leads to fewer patients receiving RRT either because death occurs before RRT initiation criteria are met or because renal recovery obviates the need for RRT. In this study, we observed that 42% of patients allocated to the delayed strategy did not receive RRT. This suggests that broader adoption of the delayed strategy may translate into reduced use of health resources. However, this did not result in fewer RRT-free days in patients allocated to a delayed strategy. This finding may be explained by the competing risk

of death: non-survivors at day 28 were attributed a zero value for RRT-free days, which decreases the power of this comparison when mortality rate is high [35].

Interestingly, each adverse event (hyperkalemia, severe bleeding, severe cardiac rhythm disorder) was infrequent and its incidence did not statistically significantly differ between strategies. This suggests that postponing RRT may be safe in the absence of life-threatening conditions.

Our meta-analysis allowed the analysis of subgroups based on baseline patient characteristics. For instance, severity of illness on admission (assessed with SOFA score) did not affect results. No statistically significant interaction for the presence of chronic kidney disease was evident. These results are at variance with those of a post-hoc analysis [36] of a previous trial [22] that suggested such patients might have a higher mortality with early RRT. Relative risks in patients with and without sepsis ruled out a possible heterogeneity of the treatment effect. Indeed, the comparison between patients with and without sepsis yielded an interaction test p value of 0.062 whereas no correction was done to account for multiplicity of comparisons. Interestingly, the STARRT-AKI trial (NCT02568722) is now completed after the enrolment of 3000 patients in an RCT on RRT initiation strategies and will examine these issues among others [37]. In addition, STARRT-AKI will provide information on long-term quality of life.

The strengths of this meta-analysis also include a comprehensive search and retrieval of all relevant trials, most being at low risk of bias, the inclusion of individual data of almost all trials, a very small number of unavailable data for the primary outcome and the focus on recent period of ICU research. Our study has limitations. In particular, it included trials that had different definitions for what constituted “early” and “delayed” RRT initiation strategies. Most studies [22–26] reported a delay of 2 to 8 hours for initiating RRT after randomization in the early strategy. By contrast, defining the delayed strategy is more difficult as some studies

used a fixed objective criterion (reaching a more severe stage of AKI [24] or a fix number of days [23]) whereas others based decision to start RRT on the occurrence of metabolic complications [22,23,25]. This resulted in noticeable variation in the timing for RRT from 25 hours [24] to 57 hours [22]. An ongoing RCT [38] is examining the possibility to further extend the delay for RRT initiation.

In conclusion, this IPDMA shows that mortality was not statistically significantly reduced by a strategy of early RRT initiation in patients with AKI. The deliberate delay of RRT initiation under close patient supervision and the initiation of RRT only when a clinical indication emerges, appears to be an acceptable approach with the potential for resource savings.

Panel: Research in context

Evidence before this study

Renal replacement therapy (RRT) is frequently used for the management of severe acute kidney injury (AKI) in critically ill patients. Although lifesaving in many situations, RRT may be associated with complications and the appropriate timing of its initiation has been a subject of intense debate. We searched MEDLINE via Pubmed, EMBASE and the Cochrane Central Register of Controlled Trials without language restriction for randomised trials evaluating different timing of RRT initiation in the context of acute kidney injury. Most of the evidence available from studies published between 2000 and 2010 came from observational studies. These older observational studies as well as study-level meta-analyses including them claimed a potential benefit for early RRT. However, observational studies did not include patients with severe AKI who never received RRT. Several authorities recently highlighted that observational studies of patients who received early or late RRT are not the adequate methodological approach and that only randomised controlled trials (RCT) comparing RRT initiation strategies could answer this hot topic question.

Several trials on RRT initiation strategies have been published in the last years. The three largest ones (AKIKI, IDEA-ICU and ELAIN) yielded conflicting results. While ELAIN trial (2016) showed a better survival outcome with early RRT, AKIKI (2016) and IDEAL-ICU (2018) did not find survival difference between early and delayed RRT initiation strategies. It was therefore crucial to perform this patient-level meta-analysis in order to have adequate statistical power to detect a modest but potentially clinically meaningful effect on mortality of one or the other strategy in the whole population and in pre-specified subgroups.

Added value of this study

This individual patient data meta-analysis of randomised clinical trials shows a high level of evidence for no statistically significant difference of mortality at day-28 (and subsequently) between delayed and early RRT initiation strategy in critically ill patients with severe acute kidney injury.

Implications of all the available evidence

In the absence of urgent indication (life-threatening metabolic complication), initiation of RRT may be safely postponed. Because delayed RRT initiation strategy entails less frequent usage of RRT by definition, one can conclude that this approach comes with the benefit of resource savings.

Contributors

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

Declaration of interests

NB is the recipient of a grant from the Société Francophone de Néphrologie, Dialyse et Transplantation for the submitted work. SMB is supported by a Canada Research Chair in Critical Care Nephrology. SMB reports receiving grant support from Baxter Healthcare Corp and speaker fees from Baxter Healthcare Corp and CAN Diagnostic Inc. RW reports receiving grant support from Baxter Healthcare Corp and speaker fees from Baxter Healthcare Corp. SG, DH, KC, SB, AC, NL, NS, TJ, GG, AD, JPQ, DD declare no competing interests

Acknowledgments

We thank all researchers, patients and surrogates involved in the individual trials. We thank Hala Alfaisal for assistance in data management. The AKIKI trial was funded by the French ministry of health. The IDEAL-ICU trial was funded by the French ministry of health. The ELAIN trial was funded by the Else-Kroner Fresenius Stiftung. The STARRT-AKI pilot trial was funded with support from the Canadian Institutes of Health Research and the University of Alberta Hospital Foundation. The HEROICS trial was funded by the French ministry of health. The HYPERDIA trial was funded by the French ministry of health. The FST trial was funded by the National Kidney Foundation of Thailand. The trial by Srisawat et al was funded by Ratchadapiseksomphot endowment fund,

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Figures legends

Figure 1: Study selection

Prisma individual patient data flow diagram

* We did not include Jamale's study for the analysis of mortality through day 28, because the database did not include the necessary information to perform this analysis

Figure 2: 28-day mortality

A: Forest plot of 28-day mortality in the intention to treat population (primary outcome)

28-day mortality was available in 8 (Combes, Wald, Gaudry, Zarbock, Barbar, Lumlertgul, Srisawat, Geri) of the 9 studies included in the individual patient data meta-analysis. This outcome was not available in the trial by Jamale et al.

CI=confidence interval.

B: Forest plot of subgroup analysis for the primary outcome

28-day mortality was available in 8 (Combes, Wald, Gaudry, Zarbock, Barbar, Lumlertgul, Srisawat, Geri) of the 9 studies included in the individual patient data meta-analysis. This outcome was not available in the trial by Jamale et al.

CI=Confidence Interval. SOFA=Sequential Organ Failure Assessment. CKD=Chronic Kidney Disease

Figure 3: Probability of survival up to day-28 in the intention to treat population according to RRT initiation strategy

Probability of survival up to day-28 was available in 8 (Combes, Wald, Gaudry, Zarbock, Barbar, Lumlertgul, Srisawat, Geri) of the 9 studies included in the individual patient data meta-analysis. This outcome was not available in the trial by Jamale et al.

HR=Hazard Ratio. CI=Confidence Interval

Table 1: **Trial characteristics, population of patients and definitions used for early and delayed RRT strategies**

	Patients n	Country	Recruitment period	Design and setting	Population characteristics (age; gender)	Experimental intervention	Criteria for RRT initiation in early strategy	Criteria for RRT initiation in delayed strategy	Time difference	RRT modality	Primary outcome	IPD obtained
Jamale et al 2013	208	India	2010-2012	Single-center trial Medical population	Age: 42 M/W%: 68/32	Early RRT strategy	SUrea concentration>25 mmol/l (or) Screatinine concentration > 619 µmol/l	Refractory hyperkalemia, Volume overload, Acidosis Uremic nausea and anorexia (judged by consensus of 2 nephrologists)	NA	IHD	Hospital mortality	Yes
STARRT pilot 2015	100	Canada	2012-2013	Multicenter trial Mixed population	Age: 63 M/W%: 72/28	Early RRT strategy	Presence of two of the following three criteria: (i) a two-fold increase in serum creatinine from baseline, (ii) urine output < 6ml/kg in the preceding 12 h, or (iii) whole-blood NGAL ≥400 ng/ml	Severe Hyperkalemia (>6 mmol/L) Severe pulmonary edema Severe metabolic acidosis (SBicar <10 mmol/L)	24	IHD CRRT SLED	Day-90 mortality	Yes
HEROICS* 2015	224 (42) *	France	2009-2012	Multicenter trial Cardiac surgery population	Age: 59 M/W%: 79/21	Early RRT strategy	Persistent post-operative shock after cardiac surgery**	Life threatening hyperkalemia KDIGO stage 3 SUrea> 36mmol/L	43	CRRT	Day-30 mortality	Yes
AKIKI 2016	619	France	2013-2016	Multicenter trial Mixed population	Age: 66 M/W%: 66/34	Delayed RRT strategy	KDIGO stage 3†	Severe Hyperkalemia (>6mmol/L) Severe pulmonary edema refractory to diuretics Severe acidosis (pH<7.15) SUrea> 40 mmol/l Oligo-anuria> 72 h	55	IHD CRRT	Day-60 mortality	Yes
ELAIN 2016	231	Germany	2013-2015	Single-center trial Surgical population	Age: 67 M/W%: 63/37	Early RRT strategy	KDIGO stage 2 ‡	KDIGO stage 3	20	CRRT	Day-90 mortality	Yes
IDEAL-ICU 2018	488	France	2012-2016	Multicenter trial Mixed population	Age: 69 M/W%: 61/39	Early RRT strategy	FAILURE stage of RIFLE §	Severe Hyperkalemia (>6.5 mmo/L) Severe pulmonary edema refractory to diuretics Severe metabolic acidosis (pH<7.15) No renal function recovery after 48 hours	45	IHD CRRT	Day-90 mortality	Yes
FST trial 2018	118	Thailand	2016-2017	Multicenter trial Mixed population	Age: 67 M/W%: 49/51	Early RRT strategy	AKI any stage of KDIGO And no response to furosemide stress test	SUrea ≥ 100 mg/dL, Severe Hyperkalemia (> 6 mmol/L) Severe metabolic acidosis (pH < 7.15)	19	CRRT	Day-28 mortality	Yes

								Severe pulmonary edema				
Srisawat et al 2018	40	Thailand	2012-2014	Multicenter trial Mixed population	Age: 67 M/W%: 55/45	Early RRT strategy	AKI any stage of RIFLE	Severe metabolic acidosis (pH<7.20) Severe Hyperkalemia (>6.2 mmo/L) Severe pulmonary edema refractory to diuretics Persistant oliguria or anuria SUrea> 40 mg/dL	48	CRRT	Day-28 mortality	Yes
HYPERDIA* 2019	35 (33) *	France	2013-2015	Single-center trial Medical population	Age: 67 M/W%: 71/29	Early RRT strategy	Post-cardiac arrest shock	Standard indications judged by physician in charge	NA	CRRT	Delay to shock resolution	Yes
Xia et al. 2019	60	China	2013-2017	Single center trial Mixed population	Age: 66 M/W%: 55/45	Early RRT strategy	Sepsis + uNGAL ≥1310 ng / ml	Severe Hyperkalemia (>6·5 mmol/L) Severe pulmonary edema Severe metabolic acidosis (pH < 7·20)	NA	CRRT	Day 28 mortality and RRT dependency	No

ICU=Intensive Care Unit. AKI=Acute Kidney Injury. RRT=Renal Replacement Therapy. KDIGO=Kidney Disease: Improving Global. M=Men. W=Women
Outcomes. IHD=Intermittent Haemodialysis. CRRT=Continuous Renal Replacement Therapy. RIFLE criteria=Risk Injury Failure Loss End stage renal disease criteria.
*Only patients with severe AKI (number in parenthesis) were included in the meta-analysis (see text for details)
† KDIGO 3 means "serum creatinine $\geq$ 3 X baseline, or increase in serum creatinine $\geq$ 4mg/dl (> 353·6 micromol/l), or urine output < 0·3 ml/kg/h for $\geq$ 24 hours or anuria for $\geq$ 12 hours"
‡ KDIGO 2 means "serum creatinine = 2·0-2·9 X baseline, or urine output < 0·5 ml/kg/h for > 12 hours"
§ FAILURE stage of RIFLE means "serum creatinine $\geq$ 3 X baseline, or increase in serum creatinine $\geq$ 4mg/dl with an acute rise > 0·5mg/dl, or urine output < 0·3 ml/kg/h for $\geq$ 24 hours or anuria for $\geq$ 12 hours)
**persistent post-operative shock was defined as requiring high dose catecholamines (epinephrine 0·2 mg/kg/min, norepinephrine. 0·4 mg/kg/min, or epinephrine + [norepinephrine/2] >0·2 mg/kg/min), or cardiovascular assistance using extracorporeal membrane oxygenation/ extracorporeal life support within 3–24 hours after intensive care unit (ICU) admission

***Table* 2: Combined baseline characteristics of the 9 randomised clinical trials included in individual patient data meta-analysis**

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

Data are mean (SD) or n/N (%)
RRT=Renal Replacement Therapy. SOFA: Sequential Organ Failure Assessment

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

	Delayed RRT strategy (n=946)	**Early RRT strategy (n=933)**	**Number of trials (number of patients included)**	**Number of missing data**	**Combined RR or mean difference (95%CI)**	I^2 (%)
28-day mortality	366/837 (44%)	355/827 (43%)	8 (1664)	7	1·01 (0·91-1·13) †	0·0
Patients who never received RRT	390/929 (42%)	-	9 (929)	17	-	-
60-day mortality	407/799 (51%)	398/784 (51%)	6 (1583)	15	0·99 (0·90-1·09) †	0·0
90-day mortality*	267/485 (55%)	260/467 (56%)	5 (952)	27	0·98 (0·83-1·16) †	45·2
Hospital mortality	412/891 (46%)	417/881 (47%)	7 (1772)	34	0·98 (0·89-1·08) †	0·0
Length of hospital stay, days	32·7 (43·9)	29·6 (40·4)	7 (1789)	17	1·8 (-3·2-6·7) ‡	61·2
RRT-free days	13·0 (12·5)	12·0 (11·7)	6 (1363)	44	1·0 (-0·3-2·2) ‡	0·0
RRT dependence at hospital discharge	39/328 (12%)	31/341 (9%)	4 (669)	20	1·34 (0·72-2·47) †	40·5
Serum creatinine§ before hospital discharge						
-All patients	115·3 (113·3)	129·3 (119·5)	8 (831)	131	4·4 (-21·8-30·7) ‡	73·5
-Patients free of RRT at hospital discharge	108·1 (74·0)	120·2 (93·7)	4 (548)	51	-15·9 (-39·4-7.5) ‡	58·2
Mechanical ventilation-free days	8·8 (10·7)	9·0 (10·7)	5 (1649)	58	-0·2 (-1·6-1·1) ‡	11·0
Vasopressor-free days	13·3 (12·0)	13·4 (12·0)	3 (1147)	2	-0·0 (-1·4-1·4) ‡	0·0

Data are mean (SD) or n/N (%)
RRT=renal replacement therapy. RR=Risk Ratio. CI: Confidence Interval.
We assessed risk ratios for binary outcomes hazard ratios for time-to-event outcomes and mean difference for quantitative outcomes
*90-day mortality was not prespecified
† RR
‡ mean difference
§ micromoles per liter

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

	Delayed RRT strategy (n=946)	**Early RRT strategy (n=933)**	**Number of trials (number of patients included)**	**Number of missing data**	**RR (95%CI)**	I^2 (%)
Adverse events						
Hyperkalemia	29/567 (5%)	20/573 (3%)	3 (1140)	9	1·52 (0·20-11·45)	72·4
Severe cardiac rhythm disorder	73/792 (9%)	61/795 (8%)	6 (1587)	11	1·20 (0·71-2·01)	49·6
Severe bleeding events	111/790 (14%)	96/785 (12%)	6 (1575)	0	1·15 (0·90-1·48)	0·0

Data are n/N (%)
RRT=renal replacement therapy. RR=Risk Ratio. CI: Confidence Interval.

Figure 1

PRISMA IPD Flow Diagram

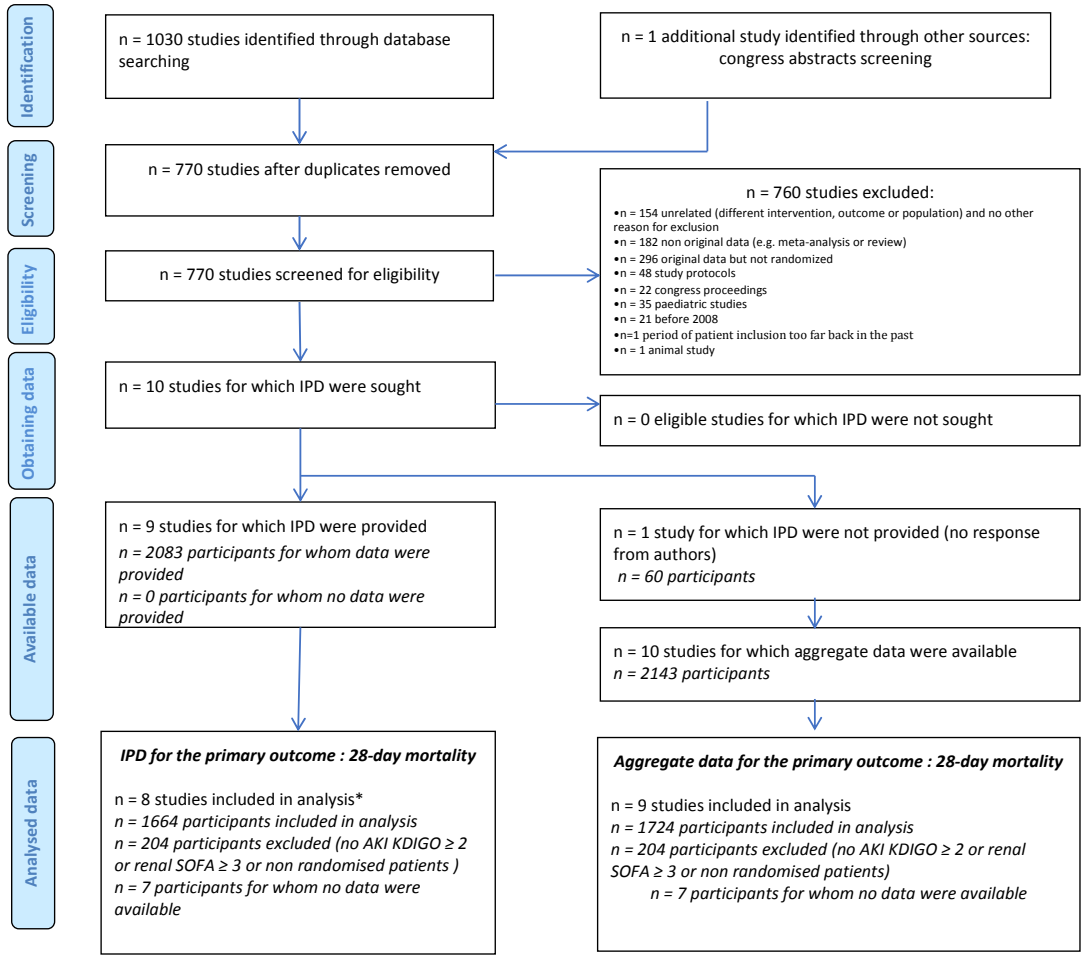

Figure 2A

28-day mortality in the intention to treat population, forest plot

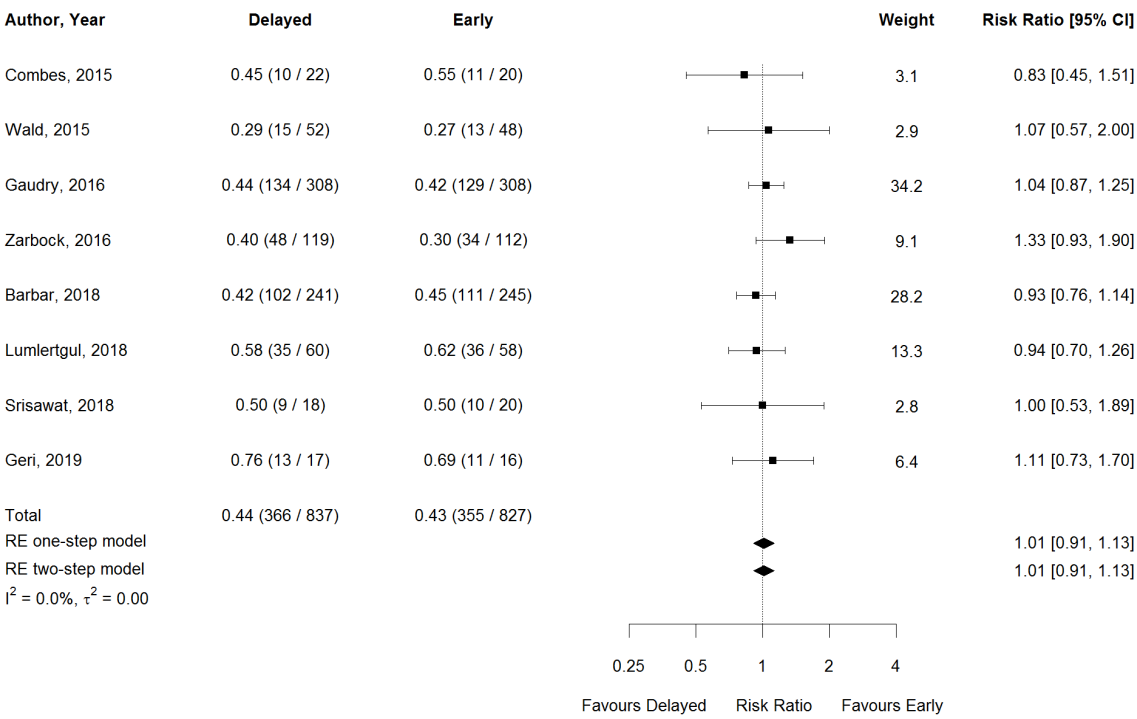

Figure 2B

Subgroup analysis for the primary outcome

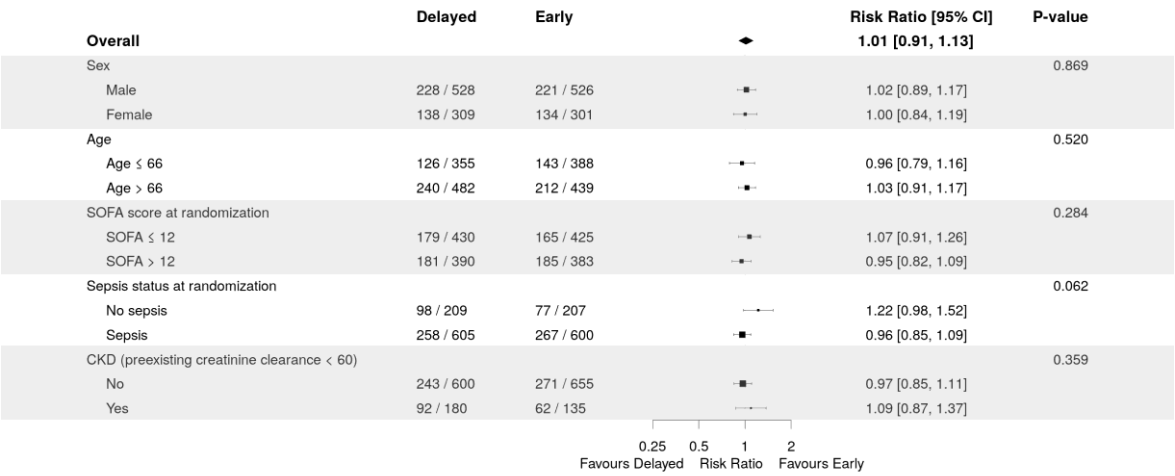

Figure 3
Probability of survival at day-28 in the intention to treat population according to RRT initiation strategy