RRT in AKI: Start Early or Wait?

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The question of when to begin RRT in patients with AKI has been debated for nearly six decades. At its inception, hemodialysis was reserved for patients facing imminent uremic death (1). Soon thereafter, the concept of prophylactic dialysis was advanced (2), and over the past half century, initiation of RRT before the onset of overt uremic symptoms has become well established. However, the optimal timing remains uncertain. Objective criteria, such as refractory hyperkalemia, intractable metabolic acidosis, and diuretic–resistant volume overload with cardiopulmonary compromise, are often absent, and the decision to begin renal support becomes one of clinical judgment (3).

The literature informing this clinical decision making has been limited. The majority of published studies have been retrospective or nonrandomized observational cohorts. Meta-analyses of these studies have suggested that earlier initiation of renal support is associated with lower mortality (4–6) and a trend toward greater recovery of kidney function (4). Interpretation of these data must be tempered, however, by the failure to include patients with early AKI who never initiated RRT, because they either recovered kidney function or died. Furthermore, attention must be paid as to how the definitions of early and late are applied when subjects with acute on CKD are included, because patients with AKI and underlying CKD who initiate RRT are at lower risk of death than patients with AKI who require RRT but have normal baseline renal function (7,8). Over the past two decades, a limited number of small randomized trials have attempted to address this question. In a trial that included 106 critically ill patients at two centers who were randomized to early high–volume hemofiltration (HVHF), early low–volume hemofiltration, or late low–volume hemofiltration, early initiation of RRT was not associated with improvement in 28-day survival or recovery of kidney function (9). In a study from India evaluating 208 patients hospitalized with community-acquired AKI who did not have an urgent indication for dialysis, a strategy of earlier initiation of dialysis was not associated with improved survival (10). Similarly, among 100 critically ill patients with Kidney Disease Improving Global Outcomes (KDIGO) stage 2 or 3 AKI included in the pilot phase of the Standard Versus Accelerated Initiation of RRT in AKI (STARRT-AKI) Trial, a planned large–scale, multicenter, randomized trial comparing strategies of accelerated and delayed initiation of RRT, there was no significant difference in 90-day survival (11).

It is in this context that the results of two randomized, controlled trials comparing accelerated with delayed initiation of RRT in critically ill patients with AKI were recently published (Table 1) (12,13). The Early Versus Late Initiation of RRT in Critically Ill Patients with AKI (ELAIN) Trial was an unblinded, single–center, randomized trial that enrolled 231 critically ill patients with KDIGO stage 2 AKI, a plasma neutrophil gelatinase–associated lipocalin >150 ng/ml, and severe sepsis, vasopressor or catecholamine dependence, refractory volume overload, or development or progression of nonrenal organ dysfunction (12). To provide rapid diagnosis and staging of AKI, serum creatinine was measured twice daily, and urine output was measured hourly. The patients were randomized to initiation of RRT either within 8 hours of diagnosis of stage 2 AKI (early), or within 12 hours of reaching stage 3 AKI or when specific metabolic and clinical indications were present (delayed) (Table 1). All 112 patients randomized to the early initiation arm and 108 of 119 patients randomized to the delayed initiation arm received RRT. The median time from diagnosis of stage 2 AKI to RRT initiation was 6.0 (interquartile range [IQR], 4.0–7.0) hours in the early arm and 25.5 (IQR, 18.8–40.3) hours in the delayed arm. Mortality at day 90 was significantly lower among patients randomized to the early initiation arm compared with those in the delayed initiation arm (39.3% versus 54.7%; hazard ratio, 0.66; 95% confidence interval [95% CI], 0.45 to 0.97; $P=0.03$). Similar benefits were observed with regard to duration of RRT and mechanical ventilation as well as hospital length of stay but not RRT dependence at day 90 among survivors or intensive care unit length of stay.

The second study, the Artificial Kidney Initiation in Kidney Injury (AKIKI) Trial, was an unblinded French multicenter, randomized trial that enrolled 620 critically ill patients who had KDIGO stage 3 AKI and were receiving invasive mechanical ventilation and/or catecholamine infusion but did not have an emergent indication for RRT (13). Patients were randomized to either initiate RRT within 6 hours of stage 3 AKI (early) or not begin RRT unless specific metabolic or clinical indications for RRT were present (delayed) (Table 1). All but six of the 311 patients randomized to the early arm received RRT, with a mean interval of 4.3 (IQR, 2.7–5.9) hours after reaching stage 3 AKI, whereas only 157 of the 308 patients (51%) randomized to the delayed arm

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Table 1. Summary of the designs and key findings of the Early Versus Late Initiation of RRT in critically ill patients with AKI Trial and the Artificial Kidney Initiation in Kidney Injury Trial

Study Characteristics	ELAIN Trial, n=231		AKIKI Trial, n=620	
No. of sites	1		31	
Enrollment criteria	KDIGO stage 2 AKI, plasma NGAL >150 ng/ml, and one of the following: severe sepsis, vasopressor/catecholamine dependence, refractory volume overload, or nonrenal organ dysfunction		KDIGO stage 3 AKI and one of the following: catecholamine infusion and/or invasive mechanical ventilation	
RRT	CVVHDF at 30 ml/kg per h		Modality/dosing at discretion of study site	
	Early RRT, n=112	Delayed RRT, n=119	Early RRT, n=311	Delayed RRT, n=308
Criteria for initiation of RRT	<8 h of Reaching KDIGO stage 2 AKI	<12 h of Reaching KDIGO stage 3 AKI, BUN>47 mg/dl, serum K^+ >6 mmol/L, serum Mg^{2+} >9.7 mg/dl, or UO<200 ml/12 h	<6 h after Reaching KDIGO stage 3 AKI	Presence of BUN>112 mg/dl, serum K^+ >6 mmol/L, pH<7.15, pulmonary edema caused by fluid overload, or oliguria or anuria >72 h
SOFA score at randomization	15.6±2.3	16.0±2.3	10.9±3.2	10.8±3.1
Received RRT (%)	112 (100)	108 (91)	305 (98)	157 (51)
Median time from KDIGO stage 2 AKI to RRT (IQR), h	6.0 (4.0–7.0)	25.5 (18.8–40.3)		
Median time from KDIGO stage 3 AKI to RRT (IQR), h			4.3 (2.7–5.9)	57 (28–83)
Serum creatinine at initiation of RRT, mg/dl	1.9±0.6	2.4±1.0	3.3±1.4	5.3±2.3
BUN at initiation of RRT, mg/dl	38±16	48±22	52±24	90±34
Serum K^+ at initiation of RRT, mmol/L	5.1±0.9	5.1±0.9	4.4±0.7	5.1±0.9
Serum tCO_2 at initiation of RRT, mmol/L	20.9±3.6	20.7±3.7	18.9±4.9	16.6±5.6
Initial modality of RRT, %				
CRRT	100	100	44	45
IHD			56	55
Mortality, %				
28 d	30.4	40.3 (P=0.11)	41.6	43.5
60 d	38.4	50.4 (P=0.07)	48.5	49.7 (P=0.79)
90 d	39.3	54.7 (P=0.03)		
Dependence on RRT among survivors (%)				
Day 28	18/78 (23.1)	26/71 (36.6; P=0.07)	22/179 (12.3)	17/178 (9.6; P=0.51)
Day 60	11/69 (15.9)	14/59 (23.7; P=0.27)	3/157 (1.9)	8/155 (5.2; P=0.12)
Day 90	9/67 (13.4)	8/53 (15.1; P=0.80)		

ELAIN, Early Versus Late Initiation of RRT in Critically Ill Patients with AKI; AKIKI, Artificial Kidney Initiation in Kidney Injury; KDIGO, Kidney Disease Improving Global Outcomes; KDIGO stage 2 AKI, more than twofold increase in serum creatinine concentration or urinary output <0.5 ml/kg per hour for ≥12 hours; NGAL, neutrophil gelatinase–associated lipocalin; KDIGO stage 3 AKI, more than threefold increase in serum creatinine concentration, serum creatinine ≥4 mg/dl with an increase of >0.5 mg/dl, or urinary output <0.3 ml/kg per hour for ≥24 hours or anuria for ≥12 hours; CVVHDF, continuous venovenous hemodiafiltration; K^+, potassium; Mg^{2+}, magnesium; UO, urine output; SOFA, sequential organ failure assessment; IQR, interquartile range; tCO_2, total carbon dioxide; CRRT, continuous RRT; IHD, intermittent hemodialysis.

received RRT, with a mean interval of 57 (IQR, 28–83) hours after reaching stage 3 AKI. Sixty-day all-cause mortality was similar in both treatment arms (48.5% in the early arm versus 49.7% in the delayed arm; adjusted hazard ratio, 1.02; 95% CI, 0.81 to 1.29; $P=0.84$); however, within the delayed RRT arm, 60-day mortality was 35.8% among patients who never initiated RRT compared with 61.8% among patients who received RRT. The number of RRT-free days was significantly higher in the delayed RRT arm, reflecting the large proportion of patients who never initiated RRT; however, there was no difference in the rates of RRT dependence in the two strategies by day 60.

How can these seemingly contradictory results be reconciled? The two studies differ in a number of key attributes. Although similar with regard to age, sex, and baseline serum creatinine, the patients in the ELAIN Trial were predominantly postsurgical (47% cardiac surgery, 34% abdominal surgery, and 12% trauma), whereas those in the AKIKI Trial were predominantly medical intensive care unit patients (80% medical and 20% surgical). Patients enrolled in the ELAIN Trial had greater severity of illness as assessed by the Sequential Organ Failure Assessment (SOFA) score (15.8±2.3 versus 10.8±3.2; $P<0.001$) but had lower rates of severe sepsis or septic shock (32% versus 72%; $P<0.001$). In addition, the management of RRT in the two studies differed. In the ELAIN Trial, RRT management was protocolized. The initial modality of RRT was continuous venovenous hemodiafiltration (CVVHDF) using a 1:1 ratio of dialysate to prefilter replacement fluid and a total effluent flow of 30 ml/kg per hour. If patients remained RRT dependent beyond 7 days, the modality could be changed to conventional intermittent hemodialysis (IHD) or prolonged intermittent RRT. In the AKIKI Trial, RRT management was not protocolized; selection of modality, dosing, and other aspects of treatment were left to the discretion of each study site and monitored in accordance with French national guidelines (14). This has led to criticism of the study and questions regarding its generalizability on the basis of use of IHD as the initial modality of RRT in 55% of patients (15); however, this was not inconsistent with the French guidelines, and the initial and subsequent modalities of RRT used were not different in the two study arms. Although limited information about the IHD prescription was presented, in prior French studies, IHD treatments have been provided with lower blood flow rates and longer treatment times than conventional IHD therapy used in the United States (16).

The most important difference between these two trials was their criteria for early and delayed RRT. Patients in the ELAIN Trial were enrolled on the basis of attainment of stage 2 AKI, and this served as the trigger for early RRT. Stage 3 AKI was the primary trigger for delayed initiation of RRT in the ELAIN Trial and for both enrollment and early initiation of RRT in the AKIKI Trial. Indeed, using severity of azotemia as a surrogate for duration of AKI, patients in the early arm of the AKIKI Trial initiated RRT later in the clinical course of AKI than patients randomized to the delayed arm of the ELAIN Trial, with higher levels of serum creatinine (3.3±1.4 versus 2.4±1.0 mg/dl; $P<0.001$) at RRT initiation. Thus, interpretation of the results of these two trials needs to be on the basis of the study-specific definitions of early and delayed RRT. The differences in the criteria for early and delayed RRT also affect how these studies relate to clinical practice. Although there is tremendous variation in criteria for initiation of RRT in patients with AKI, observational data have suggested that, in practice, very few patients with stage 2 AKI and only a minority of patients with stage 3 AKI receive RRT (17,18), suggesting that the AKIKI Trial was more closely aligned with clinical practice than the ELAIN Trial. Another striking difference between the two trials was in the number of patients randomized to delayed therapy who never initiated RRT. In the ELAIN Trial, only 11 of the 119 patients (9%) randomized to delayed RRT did not receive RRT: six patients because they did not progress from stage 2 to stage 3 AKI, four patients who recovered kidney function after reaching stage 3 AKI, and one patient for whom no RRT device was available. In the AKIKI Trial, 156 of the 308 patients (51%) randomized to the delayed arm did not progress to the protocolized criteria for initiation of RRT, although five of these patients did receive RRT. The high rate of progression from stage 2 to stage 3 AKI in the ELAIN Trial contrasts with observational data that less than one half of critically ill patients with the equivalent of stage 2 AKI progress to stage 3 AKI (17). Thus, the patients included in the ELAIN Trial may not be representative of the broader population of critically ill patients with AKI.

The difference in outcomes among the patients in the delayed arm of the AKIKI Trial who did and did not ultimately receive RRT is not unexpected. Although baseline severity of illness was similar between the early and delayed groups, within the delayed RRT arm the patients who did not progress to the prespecified criteria for RRT initiation had a lower severity of illness at baseline (median SOFA =10; IQR, 8–12) than those who reached the prespecified starting criteria and initiated RRT (median SOFA =12; IQR, 9–13). Thus, it is not surprising that mortality among patients in the late arm who ultimately required RRT was higher than in the early group and among the patients in the delayed arm who never initiated RRT. These findings are also consistent with observational studies that compared early and delayed RRT but excluded patients with AKI who never received RRT (6).

Caution must be used in evaluating relatively small, unblinded, single–center trials, such as the ELAIN Trial, in which there is an increased risk of unrecognized bias influencing observed outcomes. For example, several single–center trials of RRT dosing in critically ill patients with AKI showed similar improvements in survival with higher doses of RRT as seen with early RRT in the ELAIN Trial (19,20); however, these results were not borne out in subsequent large multicenter trials (21,22). It is also difficult to reconcile how such a relatively small difference in the timing of initiation of RRT—a difference of <1 day—resulted in not only a 34% reduction in the hazard for death but also reductions in median duration of RRT of >2 weeks and median duration of hospital stay of >4 weeks.

Finally, the results of these trials must be considered in the context of other recent clinical trials with similar study designs that explored the timing of RRT initiation in AKI. For example, the timing of RRT initiation in the ELAIN Trial is most similar to that in the High Volume Venovenous Hemofiltration Versus Standard Care for Post-Cardiac Surgery Shock (HEROICS) Trial, but the results are discordant. The HEROICS Trial was a multicenter, randomized trial of 224 patients with severe shock requiring high–dose catecholamine infusion after cardiac surgery that compared a strategy of 48

hours of HVHF initiated within 3–24 hours of surgery followed by conventional CVVHDF with standard care, in which CVVHDF was provided only for stage 3 AKI, a BUN>100 mg/dl, or life-threatening hyperkalemia (23). 111 of 112 patients in the early HVHF arm initiated RRT within 24 hours of surgery, whereas 64 of 112 patients in the conventional CVVHDF arm initiated RRT after a mean of 1.5±3.4 days. Mortality was 36% in both treatment arms at day 30 (odds ratio, 1.00; 95% CI, 0.58 to 1.73) and 46% in the early HVHF arm compared with 38% in the conventional CVVHDF arm (odds ratio, 1.34; 95% CI, 0.79 to 2.28) at day 90. As in the AKIKI Trial, 30-day mortality was lowest in the patients in the conventional CVVHDF arm who never required RRT (17%), intermediate in the patients in the early HVHF arm (40%), and highest in the patients in the conventional CVVHDF arm who met criteria for RRT (50%). In contradistinction, the results of the AKIKI Trial are concordant with the results of the pilot phase of the similarly designed STARRT-AKI Trial (11). Although this 100-patient pilot study was designed to assess the feasibility of a larger–scale multicenter, randomized trial and underpowered for definitive end point ascertainment, 90-day mortality was 38% in the accelerated RRT initiation arm compared with 37% in the delayed RRT initiation arm ($P=0.92$). Similar to the findings of the AKIKI Trial and the HEROICS Trial, 37% of individuals in the delayed initiation arm never required RRT.

How then should we proceed as clinicians and researchers in light of these two trials? The optimal timing of RRT in critically ill patients with AKI remains uncertain. Although neither trial provides a definitive answer to the question of when to start, we believe that the results of the larger, multicenter AKIKI Trial shift the balance toward a more conservative strategy with later initiation of renal support. However, the AKIKI Trial was not of sufficient size to definitively establish the noninferiority of delayed RRT. The results of other ongoing trials of timing of RRT in AKI, including the Initiation of Dialysis Early Versus Late in the Intensive Care Unit (IDEAL-ICU) Study (24) and the definitive phase of the STARRT-AKI Trial (11,25), are eagerly awaited. Until then, decisions regarding when to initiate RRT must remain based on individual patient characteristics and clinician judgment.

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References

1. Kolff WJ: First clinical experience with the artificial kidney. *Ann Intern Med* 62: 608–619, 1965
2. Teschan PE, Baxter CR, O'Brien TF, Freyhof JN, Hall WH: Prophylactic hemodialysis in the treatment of acute renal failure. *Ann Intern Med* 53: 992–1016, 1960
3. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group: KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney Int Suppl* 2: 1–138, 2012
4. Karvellas CJ, Farhat MR, Sajjad I, Mogensen SS, Leung AA, Wald R, Bagshaw SM: A comparison of early versus late initiation of renal replacement therapy in critically ill patients with acute kidney injury: A systematic review and meta-analysis. *Crit Care* 15: R72, 2011
5. Wang X, Jie Yuan W: Timing of initiation of renal replacement therapy in acute kidney injury: A systematic review and meta-analysis. *Ren Fail* 34: 396–402, 2012
6. Wierstra BT, Kadri S, Alomar S, Burbano X, Barrisford GW, Kao RL: The impact of "early" versus "late" initiation of renal replacement therapy in critical care patients with acute kidney injury: A systematic review and evidence synthesis. *Crit Care* 20: 122, 2016
7. Liaño F, Pascual J; Madrid Acute Renal Failure Study Group: Epidemiology of acute renal failure: A prospective, multicenter, community-based study. *Kidney Int* 50: 811–818, 1996
8. Mehta RL, Pascual MT, Soroko S, Savage BR, Himmelfarb J, Ikizler TA, Paganini EP, Chertow GM; Program to Improve Care in Acute Renal Disease: Spectrum of acute renal failure in the intensive care unit: The PICARD experience. *Kidney Int* 66: 1613–1621, 2004
9. Bouman CS, Oudemans-Van Straaten HM, Tijssen JG, Zandstra DF, Kesecioglu J: Effects of early high-volume continuous venovenous hemofiltration on survival and recovery of renal function in intensive care patients with acute renal failure: A prospective, randomized trial. *Crit Care Med* 30: 2205–2211, 2002
10. Jamale TE, Hase NK, Kulkarni M, Pradeep KJ, Keskar V, Jawale S, Mahajan D: Earlier-start versus usual-start dialysis in patients with community-acquired acute kidney injury: A randomized controlled trial. *Am J Kidney Dis* 62: 1116–1121, 2013
11. Wald R, Adhikari NK, Smith OM, Weir MA, Pope K, Cohen A, Thorpe K, McIntyre L, Lamontagne F, Soth M, Herridge M, Lapinsky S, Clark E, Garg AX, Hiremath S, Klein D, Mazer CD, Richardson RM, Wilcox ME, Friedrich JO, Burns KE, Bagshaw SM; Canadian Critical Care Trials Group: Comparison of standard and accelerated initiation of renal replacement therapy in acute kidney injury. *Kidney Int* 88: 897–904, 2015
12. Zarbock A, Kellum JA, Schmidt C, Van Aken H, Wempe C, Pavenstädt H, Boanta A, Gerß J, Meersch M: Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: The ELAIN randomized clinical trial. *JAMA* 315: 2190–2199, 2016
13. Gaudry S, Hajage D, Schortgen F, Martin-Lefevre L, Pons B, Boulet E, Boyer A, Chevrel G, Lerolle N, Carpentier D, de Prost N, Lautrette A, Bretagnol A, Mayaux J, Nseir S, Megarbane B, Thirion M, Forel JM, Maizel J, Yonis H, Markowicz P, Thiery G, Tubach F, Ricard JD, Dreyfuss D; AKIKI Study Group: Initiation strategies for renal-replacement therapy in the intensive care unit. *N Engl J Med* 375: 122–133, 2016
14. Vinsonneau C, Allain-Launay E, Blayau C, Darmon M, Ducheyron D, Gaillot T, Honore PM, Javouhey E, Krummel T, Lahoche A, Letacon S, Legrand M, Monchi M, Ridel C, Robert R, Schortgen F, Souweine B, Vaillant P, Velly L, Osman D, Van Vong L: Renal replacement therapy in adult and pediatric intensive care : Recommendations by an expert panel from the French Intensive Care Society (SRLF) with the French Society of Anesthesia Intensive Care (SFAR) French Group for Pediatric Intensive Care Emergencies (GFRUP) the French Dialysis Society (SFD). *Ann Intensive Care* 5: 58, 2015
15. Mehta RL: Renal-replacement therapy in the critically ill–does timing matter? *N Engl J Med* 375: 175–176, 2016
16. Vinsonneau C, Camus C, Combes A, Costa de Beauregard MA, Klouche K, Boulain T, Pallot JL, Chiche JD, Taupin P, Landais P, Dhainaut JF; Hemodiafe Study Group: Continuous venovenous haemodiafiltration versus intermittent haemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: A multicentre randomised trial. *Lancet* 368: 379–385, 2006
17. Hoste EA, Clermont G, Kersten A, Venkataraman R, Angus DC, De Bacquer D, Kellum JA: RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: A cohort analysis. *Crit Care* 10: R73, 2006
18. Hoste EA, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, Edipidis K, Forni LG, Gomersall CD, Govil D, Honoré PM, Joannes-Boyau O, Joannidis M, Korhonen AM, Lavrentieva A, Mehta RL, Palevsky P, Roessler E, Ronco C, Uchino S, Vazquez JA, Vidal Andrade E, Webb S, Kellum JA: Epidemiology of acute kidney injury in critically ill patients: The multinational AKI-EPI study. *Intensive Care Med* 41: 1411–1423, 2015
19. Ronco C, Bellomo R, Homel P, Brendolan A, Dan M, Piccinni P, La Greca G: Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: A prospective randomised trial. *Lancet* 356: 26–30, 2000
20. Saudan P, Niederberger M, De Seigneux S, Romand J, Pugin J, Perneger T, Martin PY: Adding a dialysis dose to continuous

hemofiltration increases survival in patients with acute renal failure. *Kidney Int* 70: 1312–1317, 2006
21. Palevsky PM, Zhang JH, O'Connor TZ, Chertow GM, Crowley ST, Choudhury D, Finkel K, Kellum JA, Paganini E, Schein RM, Smith MW, Swanson KM, Thompson BT, Vijayan A, Watnick S, Star RA, Peduzzi P; VA/NIH Acute Renal Failure Trial Network: Intensity of renal support in critically ill patients with acute kidney injury. *N Engl J Med* 359: 7–20, 2008
22. Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, Lo S, McArthur C, McGuinness S, Myburgh J, Norton R, Scheinkestel C, Su S; RENAL Replacement Therapy Study Investigators: Intensity of continuous renal-replacement therapy in critically ill patients. *N Engl J Med* 361: 1627–1638, 2009
23. Combes A, Bréchot N, Amour J, Cozic N, Lebreton G, Guidon C, Zogheib E, Thiranos JC, Rigal JC, Bastien O, Benhaoua H, Abry B, Ouattara A, Trouillet JL, Mallet A, Chastre J, Leprince P, Luyt CE: Early high-volume hemofiltration versus standard care for post-cardiac surgery shock. The HEROICS Study. *Am J Respir Crit Care Med* 192: 1179–1190, 2015
24. Barbar SD, Binquet C, Monchi M, Bruyère R, Quenot JP: Impact on mortality of the timing of renal replacement therapy in patients with severe acute kidney injury in septic shock: The IDEAL-ICU study (initiation of dialysis early versus delayed in the intensive care unit): Study protocol for a randomized controlled trial. *Trials* 15: 270, 2014
25. Smith OM, Wald R, Adhikari NK, Pope K, Weir MA, Bagshaw SM; Canadian Critical Care Trials Group: Standard versus accelerated initiation of renal replacement therapy in acute kidney injury (STARRT-AKI): Study protocol for a randomized controlled trial. *Trials* 14: 320, 2013

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