Timing of renal replacement therapy in critically ill patients: where are the hands on the clock?

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Renal replacement therapy (RRT) is a key component in the management of acute kidney injury (AKI) in the intensive care unit (ICU). Whilst most studies in critically ill patients have focused primarily on RRT methods and modalities, no consensus exists on optimal timing of RRT initiation. There is agreement to start up RRT as soon as possible in the presence of life-threatening fluid overload, hyperkalemia, uremia, or metabolic acidosis (1). However, the ideal timing of RRT to treat AKI that is not accompanied by urgent clinical or metabolic complications is still debated. Some experts promote early initiation to assure immediate adequate control of metabolic, fluid, and pro-inflammatory parameters. Adepts of a delayed initiation strategy adhere to more in-depth diagnostic and therapeutic "fine-tuning" which could even obviate the need for RRT. Benefits of each approach must, of course, be outweighed against potential risks such as "overshoot" dialysis and hemodynamic complications associated with an early initiation protocol or worsening metabolic and clinical status (when RRT is "postponed"). Earlier institution of RRT in critically ill patients with AKI is thought to have a beneficial impact on survival. However, this conclusion is mainly based on heterogeneous studies of variable quality (2).

Two recently published prospective randomised trials have assessed the impact of different timing of RRT on the outcome of severely ill ICU patients with AKI devoid of acute life-threatening complications. The Artificial Kidney Initiation in Kidney Injury (AKIKI) study (3) found no significant difference in 60-day mortality between an early and delayed RRT strategy (48.5% *vs.* 49.7%; P=0.79). Catheter-related infection occurred less frequently in the delayed treatment arm. Though not addressed as a side-effect, hypophosphatemia was more prevalent in early treated patients. Length of ICU and hospital stay was not different between groups. Interestingly, half (!) of the patients allotted to delayed treatment did not require RRT. Hemodynamic target values or fluid volumes were either not defined or provided which implies that some patients may have faced transient AKI due to inadequate cardiovascular resuscitation. In contrast, the early versus late initiation of RRT in critically ill patients with AKI (ELAIN) trial (4) reported a significantly reduced 90-day mortality in patients receiving early as compared with delayed RRT (39.3% *vs.* 54.7%; P=0.03). Early initiation of RRT resulted in a more rapid recovery of renal function, significantly shortened duration of hospitalisation, but did not affect future dialysis dependence or length of ICU stay.

How do these studies contribute to a more optimal RRT timing strategy in critically ill patients who develop AKI? The answer is painfully simple: very little! Many relevant incoherencies and flaws seriously challenge the clinical impact of the (combined) AKIKI and ELAIN study results. First, the editorials accompanying each study (5,6) already pointed to a discrepancy in "early" and "delayed" RRT connotation. Following randomization, patients in the ELAIN trial received delayed treatment more "early" than their AKIKI counterparts (<24 *vs.* >50 h). The modest difference in RRT initiation time in the ELAIN trial is also difficult to reconcile with the strikingly positive effects on outcome. Second, salient differences between the AKIKI and ELAIN study concepts must be underlined. The AKIKI trial was a multicenter trial conducted in 31 ICUs screening 5,528 predominantly medical patients for 29 months to finally randomize 620 (11%) subjects.

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The ELAIN trial was a single-center trial conducted for 23 months screening 604 almost exclusively postsurgical and trauma patients to include 231 (38%) subjects. This suggests potential patient selection, inclusion, and treatment bias. Third, in line with the previous concern, it is obvious that both trials included patients at a different stage of AKI. Both studies used the Kidney Disease Improving Global Outcomes (KDIGO) classification for AKI staging. All AKIKI patients were included at KDIGO stage 3 AKI. In the ELAIN trial, early RRT was initiated within 8 h of diagnosis of KDIGO stage 2 AKI and delayed RRT within 12 h of KDIGO stage 3. From a clinical viewpoint, this implies that all patients entering the AKIKI trial had "renal failure (or worse)" whereas this was only the case for the delayed ELAIN group. Patients receiving early treatment in the ELAIN trial were thus included with "less severe" AKI, which could have beneficially influenced outcome. This is corroborated by earlier studies comparing standard continuous RRT with either intermittent hemodialysis (IHD) (7) or high-volume hemofiltration (8) which reported respectively 67% and 49.3% 60-day mortality in the continuous RRT study arm. This huge difference in mortality was not explained by a baseline divergence in patient population, severity of disease, comorbidities, or degree of organ failure but was most likely determined by initiating RRT at "failure" (7) versus "injury" level (8). Fourth, RRT modalities substantially differed between both studies. All patients in the ELAIN trial underwent continuous RRT in veno-venous hemodiafiltration mode. In contrast, continuous RRT was applied in only 30% of the AKIKI patients. It was not specified which AKIKI patients received continuous RRT, what mode was used, and whether continuous RRT was provided at an earlier or later stage of the study. Continuous RRT has not been shown to improve mortality or to ward off dialysis dependency but may be beneficial for patients with severe fluid-overload or unstable cardiogenic/septic shock (9). After receiving continuous RRT, ELAIN subjects in both the early and delayed group were transitioned to daily sustained low-efficiency dialysis whereas this technique was never used in AKIKI patients. Moreover, half of the AKIKI subjects were primarily treated with IHD. IHD is often complicated by hypotension caused by too rapid fluid removal. IHD-associated intravascular volume depletion and decrease in cardiac output may severely impair tissue perfusion even in the absence of overt clinical signs (10). Differences in fluid dynamics between IHD and continuous RRT may also considerably determine individual hemodynamic assessment and treatment. Thus, an imbalanced choice favouring a particular RRT technique may have significantly influenced outcome data in the AKIKI study, in particular because this trial included a majority of septic shock patients. Finally, both trials included a comparable number of patients receiving mechanical ventilation and/or vasopressor support at baseline. Vasopressor- and ventilator-free days were not significantly different between early and delayed treatment groups in the AKIKI study. In the ELAIN study, however, the delayed RRT group was longer ventilated and showed a trend towards persistent cardiovascular dysfunction (respectively P=0.002 and P=0.12 as compared with early RRT). The ELAIN survival curves started to separate at day 5 from study inclusion. At that time, more patients in the delayed RRT arm were ventilator-dependent and probably still in need of more intensive cardiovascular support, both of which are associated with a compromised outcome.

In conclusion, we highly estimate and applaud the information provided by the rigorously conducted AKIKI and ELAIN trials. However, we must not remain blind to the many hidden pitfalls and apparent shortcomings which cloud the interpretation of study results and cast reasonable doubt on their clinical utility at the bedside. We strongly support the KDIGO classification for AKI but meaningful outcome results will only be obtained when patients are entered at comparable KDIGO stages, especially when initiation of RRT is time-related.

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Footnote

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References

1. Ostermann M, Dickie H, Barrett NA. Renal replacement

therapy in critically ill patients with acute kidney injury--when to start. Nephrol Dial Transplant 2012;27:2242-8.

2. Karvellas CJ, Farhat MR, Sajjad I, et al. 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 2011;15:R72.

3. Gaudry S, Hajage D, Schortgen F, et al. Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit. N Engl J Med 2016;375:122-33.

4. Zarbock A, Kellum JA, Schmidt C, et al. 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 2016;315:2190-9.

5. Chertow GM, Winkelmayer WC. Early to Dialyze: Healthy and Wise? JAMA 2016;315:2171-2.

6. Mehta RL. Renal-Replacement Therapy in the Critically Ill--Does Timing Matter? N Engl J Med 2016;375:175-6.

7. Vinsonneau C, Camus C, Combes A, et al. Continuous venovenous haemodiafiltration versus intermittent haemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: a multicentre randomised trial. Lancet 2006;368:379-85.

8. Joannes-Boyau O, Honoré PM, Perez P, et al. High-volume versus standard-volume haemofiltration for septic shock patients with acute kidney injury (IVOIRE study): a multicentre randomized controlled trial. Intensive Care Med 2013;39:1535-46.

9. Truche AS, Darmon M, Bailly S, et al. Continuous renal replacement therapy versus intermittent hemodialysis in intensive care patients: impact on mortality and renal recovery. Intensive Care Med 2016. [Epub ahead of print].

10. Jakob SM, Ruokonen E, Vuolteenaho O, et al. Splanchnic perfusion during hemodialysis: evidence for marginal tissue perfusion. Crit Care Med 2001;29:1393-8.