Editorial

Timing of renal replacement therapy in acute kidney injury—an issue of importance?

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Submitted Jun 30, 2016. Accepted for publication Jul 07, 2016.
doi: 10.21037/jtd.2016.08.09
View this article at: http://dx.doi.org/10.21037/jtd.2016.08.09

Acute kidney injury is a common complication in critically ill patients associated with an increased morbidity and mortality (1). It manifests itself in approximately 50% of critically ill patients, and it is, in cases of higher degrees of severity or combinations with other organ failures, associated with mortality rates exceeding 40% (2). Up to now therapeutic options are restricted to the use of symptomatic renal replacement therapy in patients with life-threatening fluid accumulation or greater imbalances or disruptions in homeostasis (3). However, even the optimal management of renal replacement therapy remains elusive (3,4).

Several well-designed studies have been carried out during the last years to clarify some of the issues related to renal replacement therapy, including the dose to be administered (5). But the key question is when to initiate renal replacement therapy in critically ill patients with evolving acute kidney injury. Starting renal replacement therapy early could offer benefits, but inevitably results in an escalation of therapy. The guidelines for acute kidney injury recommend to initiate renal replacement therapy emergently when life-threatening changes in fluid, electrolyte and acid-base balance exist or when a progressive decline of kidney function coincides with any serious worsening of a patients clinical condition (3). These guidelines leave the final decision to initiate or not to initiate renal replacement therapy to the arbitrary decision of the treating physician. In an effort to remedy the problem, few small prospective studies have been performed during the last years. Most of these studies demonstrated that early initiation of renal replacement therapy in critically ill patients with acute kidney injury has a beneficial effect on patient-relevant outcomes (6-9). A meta-analysis which includes retrospective and observational trials also indicated a survival benefit for early initiation of renal replacement therapy (10). However, these conclusions are based on heterogeneous studies of generally low methodical quality. A recently published meta-analysis including only studies which with high quality criteria, found no significant difference between early and late initiation of renal replacement therapy (11). However, contrary to the intention of the authors and similarly to previous meta-analyses, the trials were characterized by statistically high heterogeneity which makes same hard to compare.

Lately, Gaudry *et al.* reported in the *New England Journal of Medicine* on the results from the multicenter Artificial Kidney Initiation in Kidney Injury (AKIKI) trial examining the effects of early versus delayed strategy for the initiation of renal replacement therapy in 620 critically ill patients with severe acute kidney injury treated in 31 intensive care units in France (12). Adult patients (age >18 years) on the intensive care unit receiving mechanical ventilation, vasopressor therapy (epinephrine or norepinephrine) or both were screened. Patients were eligible to be randomized once they achieved stage 3 of acute kidney injury according to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines. KDIGO stage 3 is defined as follows: serum-creatinine >4 mg/dL or >3 times baseline serum-creatinine, anuria (urinary output of 100 mL/day or less) for >12 hours or oliguria (urinary output <0.3 mL/kg/h or <500 mL/day) >24 hours. Patients were excluded if they had life-threatening complications requiring immediate initiation of renal replacement therapy (e.g., hyperkalemia, poisoning), pre- and postrenal causes for acute kidney injury, previous renal replacement therapy due to acute kidney injury, previous

kidney transplant and pre-existing severe chronic renal insufficiency (defined as creatinine clearance <30 mL/min).

Patients were randomly assigned to receive either early (start of renal replacement therapy within 6 hours after documentation of acute kidney injury stage 3) or delayed (start if patients had severe hyperkalemia, uremia, metabolic acidosis, pulmonary edema, or severe oliguria persisting for more than 72 hours after randomization) strategy. The primary endpoint was 60-day all-cause mortality.

Of the 620 patients enrolled, 306 of 312 patients (98.1%) in the early and 157 of 308 patients (51.0%) in the delayed group received renal replacement therapy. In both groups more than 50% received intermittent renal replacement therapy as first modality. Mortality after 60 days was 48.5% [95% confidence interval (CI): 42.6 to 53.8] in the early versus 49.7% (95% CI: 43.8 to 55.0) in the delayed group (P=0.79). However, 49% of the patients in the delayed group never received renal replacement therapy. Analyzing only those patients who received renal replacement therapy, mortality at 60 days was 48.5% in the early and 61.8% in the delayed group. Those patients never receiving renal replacement therapy had lowest mortality (37.1%), but were less ill at baseline compared to the other groups as shown by SOFA scores (P<0.0001).

Concurrently with Gaudry's publication, Zarbock *et al*. reported in the *JAMA* on findings from a single-center trial in Germany analyzing the effect of early versus delayed initiation of renal replacement therapy in critically ill patients with acute kidney injury (13). Patients were eligible for randomization once they reached stage 2 acute kidney injury according to the KDIGO guidelines. KDIGO stage 2 is defined as 2-times increase in serum-creatinine from baseline and/or urinary output of <0.5 mL/kg/h for at least 12 hours. Furthermore, inclusion required one of the following additional criteria: severe sepsis/septic shock, use of high vasopressor doses, refractory fluid overload or progression of non-renal organ dysfunction (non-renal SOFA score >2). To exclude those patients who have a high likelihood of spontaneous recovery from acute kidney injury, the authors implemented measurements of plasma neutrophil gelatinase-associated lipocalin (NGAL) in their study protocol. NGAL is a well established biomarker of renal injury, as it has consistently been demonstrated that patients with plasma levels of NGAL below 150 ng/mL will not require renal replacement therapy (14,15). Consequently only patients with plasma NGAL levels >150 ng/mL were eligible for inclusion. Exclusion criteria were largely similar to those of the AKIKI trial.

Patients with KDIGO stage 2 acute kidney injury and plasma NGAL levels >150 ng/mL were then randomly assigned to one of the two treatment arms: early initiation of renal replacement therapy within 8 hours after reaching KDIGO stage 2 and delayed initiation of renal replacement therapy within 12 hours after reaching KDIGO stage 3. To standardize the therapeutic procedure all patients primarily underwent continuous renal replacement therapy with blood flow kept above 110 mL/min and a prescribed effluent dose of 30 mL/kg/h, according to the KDIGO recommendations. Continuous renal replacement therapy was maintained for at least 7 days, unless cessation criteria were satisfied over that period, before changing to an intermittent procedure. Patients were followed for the primary endpoint 90-day all-cause mortality.

Of the 231 patients enrolled, 112 of 112 (100%) in the early and 108 of 119 (90.8%) patients in the delayed group received renal replacement therapy. According to the protocol, 100% of the included patients were treated with continuous renal replacement therapy as first modality, according to the protocol. Mortality after 90 days was 39.9% in the early and 54.7% in the delayed group (P=0.03). Moreover, for various secondary endpoints statistically significant clinical benefits, encouraging the early initiation of renal replacement therapy, were observed: duration of renal replacement therapy, mechanical ventilation, hospital-length of stay and recovery of renal function at day 90 (defined as dialysis independency) were significantly shorter in the early group.

The interpretation and comparison of the two studies is limited due to considerable differences in study designs. The crucial difference is the time at which renal replacement therapy was initiated. This is important, as acute kidney injury is a systemic disease affecting inflammation and function of different organs (16). Against this background it can be speculated that early treatment attenuates pro-inflammatory effects and a further decline in other organs function (17). Patients assigned to the early group in the AKIKI trial are almost identical with, but at least very similar to the patients assigned to the late group in the ELAIN trial. Because mortality rates are comparably high in these two groups, awareness should be raised that the initiation of renal replacement therapy at stage 3 of acute kidney injury might be too late to improve patients' outcome. Another important difference concerns the execution of renal replacement therapy. Fifty five percent of the AKIKI patients received intermittent renal replacement therapy, whereas all patients in the ELAIN trial received

continuous renal replacement therapy. Since most of the patients in the AKIKI trial needed vasopressor therapy, the question arises whether the intermittent nature of renal replacement therapy with its resultant negative effects on hemodynamic stability might have contributed to the mortality rate (18). Another difference between AKIKI and ELAIN exists with regard to the degree of severity of the disease. Patients in the AKIKI trial were less ill than patients in the ELAIN trial as demonstrated by lower SOFA scores (SOFA 11 *vs.* SOFA 16, respectively). This may further distort comparability of the results.

Despite these differences, both studies present interesting results which help clarify whether and to what extent early initiation of renal replacement therapy has the potential to improve patients' outcome. For future studies there is a need to integrate new biomarkers in the study design, in an effort to more effectively prognosticate the clinical course and progression of acute kidney injury (19) and to better predict the need for renal replacement therapy (20,21). However, to improve the performance of biomarkers in clinical scenarios, it is important to measure biomarkers only in patients with a certain risk profile (22). Furthermore, investigators are requested to focus not only on mortality, but to place more rigorously emphasis on renal recovery and progression of acute kidney injury to chronic kidney disease (CKD) and end stage renal disease, as it has been shown that patients who survive an episode of acute kidney injury have an increased risk to develop CKD (23). Future studies should also consider the question of whether the timing of renal replacement therapy impacts on renal recovery defined by serum creatinine and albuminuria. Moreover, it is important to use standardized definition models, ideally the latest KDIGO criteria, to achieve comparable results. Risk-stratification concepts will be necessary to find the optimal strategy for initiation.

Two large multi-center trials are under way [STARRT-AKI (24) and IDEAL-ICU (25)]. Unfortunately, these studies do not integrate biomarkers in their study design, but will hopefully provide new insights for the initiation of renal replacement therapy in critically ill patients with acute kidney injury.

Acknowledgements

Funding: This work was supported by the Deutsche Forschungsgemeinschaft (ZA428/10-1 to A.Z.)

Footnote

Provenance: This is an invited Editorial commissioned by the Section Editor Zhiheng Xu (State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, Department of Intensive Care, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China).
Conflicts of Interest: AZ has received grant support and lecture fees from Astute Medical and lecture fees from Fresenius. MM received lecture fees from Astute Medical.

Comment on: 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.

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Cite this article as: Meersch M, Zarbock A. Timing of renal replacement therapy in acute kidney injury—an issue of importance? J Thorac Dis 2016;8(9):2301-2304. doi: 10.21037/jtd.2016.08.09

