Editorial

When to start a renal replacement therapy in acute kidney injury (AKI) patients: many irons in the fire

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In 2012, the Kidney Disease Improving Global Outcomes (KDIGO) guidelines have been released and detailed and graded recommendations concerning all the aspects of critical care nephrology (1). One of the chapters is specifically dedicated to "Dialysis Interventions for Treatment of acute kidney injury (AKI); Timing of renal replacement therapy (RRT)". Even if the question on when to start RRT is constantly solicited by nephrologists and intensivists in case of severe AKI (2), KDIGO guidelines only provided expert opinion statements: "*Initiate RRT emergently when life-threatening changes in fluid, electrolyte, and acid-base balance exist* (*Not Graded*)" and "*Consider the broader clinical context, the presence of conditions that can be modified with RRT, and trends of laboratory tests—rather than single BUN and creatinine thresholds alone—when making the decision to start RRT* (*Not Graded*)" (1). In current clinical practice, the decision to start RRT is based on the development of volume overload, not responding to diuretics, and biochemical features of solute imbalance (azotemia, hyperkalemia, severe acidosis): these indications may lead the physicians to avoid dialysis as long as possible with the aim of giving time to spontaneous recovery of renal function and of avoiding the risks associated with RRT (1), including chronic renal dysfunction (3). On the other side, promoters of anticipated RRT start may be indicating dialysis in patients who would not have needed it. Given this range of uncertainty, a single-center randomized trial, specifically designed to evaluate early initiation of RRT in critically ill patients with AKI, has been recently published in the *Journal of American Medical Association* (*JAMA*) by Zarbock and co-workers (4): the Early or deLAyed Initiation of RRT (ELAIN) trial. This study showed that 90-day all-cause mortality is significantly reduced by early RRT start. Interestingly, another similar (early *vs.* delayed RRT strategy) bigger multi-center randomized trial, by Gaudry *et al.* on the *New England Journal of Medicine* (*NEJM*) failed to reach the benefit in overall survival at day 60 as primary outcome (5): the Artificial Kidney Initiation in Kidney Injury (AKIKI) trial. Due to the different results, the two studies have to be critically analyzed before reaching any final conclusion. The aim of the present editorial is to analyze the main differences, strengths and limitations of the two studies and to finally summarize some critical conclusions.

AKI severity (stage) at randomization represents the most evident difference between ELAIN and AKIKI. KDIGO stage 2 is reached when serum creatinine increases 2.0–2.9 times baseline level or urine output (UO) decreases below 0.5 mL/kg/h for 12 hours, while KDIGO stage 3 is reached when serum creatinine increases 3.0 times the baseline level or above 4.0 mg/dL or UO decrease below 0.3 mL/kg/h for 24 hours or anuria is present for ≥12 hours. In the *JAMA* study, indications to start RRT were: KDIGO stage 2; plasma neutrophil gelatinase-associated lipocalin (NGAL) >150 ng/mL; one of the following: severe sepsis, use of vasopressors or catecholamines, refractory fluid overload, development or progression of non-renal organ dysfunction [Sequential Organ Failure Assessment

(SOFA) score ≥2]. In the *NEJM* study, the patients had to reach the stage 3 criteria to be enrolled in the trial (*Table S1*). Therefore, at first sight, when the two studies are compared it is clear that the level of renal severity was significantly different. According to this consideration, Gaudry *et al.*, when listing the limitations of the study, clearly underlined that the AKI severity of enrolled patients was advanced and, therefore, the observed results may not be generalizable to patients with lower KDIGO stages.

Second, substantial differences in "early" and "delayed" definitions differentiate the two studies (*Table S1*). The "early" arm in the *JAMA* study was composed by patients treated by RRT within 8 hours from stage 2 AKI while in the *NEJM* treatment was delivered as soon as the patient reached a stage 3 AKI plus need of mechanical ventilation (MV), or catecholamines, or both. The "delayed" group in the *JAMA* study implied RRT start within 12 hours of diagnosis of stage 3 or any of the following: serum urea level higher >100 mg/dL; hyperkalemia (>6 mEq/L) and/or with electrocardiography abnormalities; serum magnesium level >8 mEq/L; UO <200 mL/12 hours or anuria; and organ edema in the presence of AKI resistant to diuretic treatment (one attempt with loop diuretics prior to randomization). In the *NEJM* study "delayed" patients started RRT when one of the following conditions was reached: severe hyperkalemia, metabolic acidosis, pulmonary edema, BUN >112 mg/dL, anuria or oliguria >72 hours after randomization. These different definitions of "early" and "delayed" timing and, therefore, in clinical severity, need a further comment: it is possible that early patients of the ELAIN trial were the less severe ones and it is probably not surprising that their outcomes were significantly improved. At the bedside, it is unlikely that a KDIGO stage 2 patient, outside a rigid randomization protocol, would be ever considered for RRT.

Another key point that deserves a comment is that more than 50% of the patients in the *NEJM* study received intermittent hemodialysis (IHD) as the first method of therapy and only 30% of them received continuous renal-replacement therapy (CRRT) as the sole method (with no intermittent dialysis at any time). In respect of this point, the KDIGO guidelines (1) suggest to "*use continuous and intermittent RRT as complementary therapies in AKI patients. (Not graded)*" but "*suggest using CRRT, rather than standard intermittent RRT, for hemodynamically unstable patients (2B)*". In light of this aspect and taking into consideration that in the *NEJM* study vasopressor support with epinephrine or norepinephrine was necessary in 85% of both groups, such a wide application of IHD might imply some concerns on patients' outcomes. It must be acknowledged, however, that centers routinely applying IHD to critically ill patients are generally able to manage those with hemodynamic instability. Still, generalizability of AKIKI trial results might be argued in those centers only applying CRRT. Much differently in the Zarbock *et al.*'s study all the patients were exclusively treated with CRRT with a precise treatment protocol (predilution; dialysate to replacement fluid =1:1; dose 30 mL/kg/h, blood flow >110 mL/min, citrate for anticoagulation). The application of a precise and homogenous protocol is a consistent strength that should be considered: this is likely due to the fact that a single-center study does not have to take into consideration multiple institutions' choices and preferences. However, in the AKIKI trial RRT prescription was not pre-specified and the role of RRT dose in affecting outcomes of early and delayed treatments remains unsolved.

A huge difference between the studies is also represented by the primary outcome: in a total of 231 patients the Zarbock *et al.*'s study showed an overall mortality at 90-day follow-up of 39.3% (44/112) in the early group and 54.7% (65/119) in the delayed group (P=0.03; between-group difference, –15.4%). Differently, in the Gaudry *et al.*'s study an early RRT failed to demonstrate any benefit of early *vs.* delayed strategy since the 60-days mortality rate was 58.5% in the early group and 49.7% in the delayed group (P=0.79) (*Table S1*). Noteworthy, most of the secondary outcomes were reached in Zarbock *et al.*'s study further suggesting the advantages of starting RRT early (e.g., duration of RRT, recovery of renal function, duration of mechanical ventilation, length of hospital and intensive care unit (ICU) stay, requirement of RRT at day 90, decrease in IL-6 and IL-8 plasma concentration) (*Table S1*). Similarly to the primary outcome, the main secondary outcomes were not reached in the Gaudry *et al.*'s study and, in addition, bloodstream catheter infection and hypophosphatemia resulted worst in the early group (P=0.03 for both). Interestingly, in the AKIKI trial, 49% of patients enrolled in the delayed arm did not receive any RRT (compared to 9% in the ELAIN). Moreover, it should be underlined that, in Gaudry *et al.*'s study, the lowest mortality at day 60 (37.1%) was found among patients who never received RRT, and the highest mortality (61.8%) was found among those who received therapy late, whereas intermediate mortality (48.5%) was found among patients who received therapy early (P<0.001). Patients in the delayed-strategy group who never received dialysis

were less ill at baseline, and patients who received it late were the most severely ill patients at baseline. Moreover, the differences in mortality became nonsignificant after adjustment for baseline severity of illness. These aspects strongly suggest the importance of RRT timing with respect to severity of illness: if it is might be true that in the "average" patient the effect of RRT timing in mortality is diluted, it is also true that the "average" patient does not exist in the real world. It is certain that the most severely critically ill patients have to be aggressively and timely treated in order to attempt a change of their clinical history.

Discontinuation strategy is another key aspect in the management of patients treated with RRT. Current literature is quite blurred also in this field of acute RRT. KDIGO guidelines' criteria (1) for stopping RRT in AKI state: "*Discontinue RRT when it is no longer required, either because intrinsic kidney function has recovered to the point that it is adequate to meet patient needs, or because RRT is no longer consistent with the goals of care. (Not Graded)*" and "*We suggest not using diuretics to enhance kidney function recovery, or to reduce the duration or frequency of RRT (2B)*". Discontinuation strategy also slightly differed in Gaudry *et al.*'s and Zarbock *et al.*'s studies: in the first one, in both groups, discontinuation of RRT was considered if the spontaneous UO was >500 mL/24 hours and it was highly recommended if the spontaneous UO was higher than 1,000 mL per 24 hours in the absence of diuretic therapy or if UO was >2,000 mL per 24 hours in patients who were receiving diuretic therapy and mandatory if diuresis was sufficient to allow for spontaneous decrease in serum creatinine concentration. In Zarbock *et al.*'s study, renal recovery was defined by UO >400 mL/24 hours without and 2,100 mL/24 hours with diuretic treatment and creatinine clearance >20 mL/min. The ideal threshold for RRT discontinuation is clearly a fundamental aspect for evaluation of therapy efficacy.

Based on the observed results, the first novel element we should appreciate is that both studies feasibly and quite easily achieved the "early RRT": it is currently possible to anticipate RRT, if indicated. Then it could be hypothesized that early initiation of RRT may lead to clinical benefits by quickly controlling the metabolic or uremic derangements, by preventing the deleterious effects of fluid overload and by attenuating kidney-specific and non-kidney organ injury (e.g., inflammatory damage). According to Zarbock *et al.*, using a combination of the KDIGO classification system and the plasma NGAL concentration may be of help in detecting those patients that most probably benefit from early RRT. On the other side, even if Gaudry *et al.*'s conclusions were against the benefit of early RRT initiation and that the recovery of renal function (identified by diuresis), was more rapid in the delayed-strategy group than in the early-strategy group, the authors cleverly concluded that their study suggests a careful surveillance of each case to decide when RRT should be started with a benefit-to-risk ratio approach.

It is our personal consideration that, although both studies have been conducted on a large population of patients, with high level scientific methodology and with rigorous study designs, the significant differences in the various characteristics of the two studies suggest great attention before reaching any conclusion about early or late RRT benefits in patients with AKI. Patients with AKI, admitted or not to the ICU, clearly have very different origins of kidney damage with variable degrees of organs involvement with a variable degrees of severity: some have multiorgan failure with underlying severe coexisting comorbidities and they might have significantly different clinical courses from post-surgical patients with AKI or isolated organ dysfunction. Careful stratification based on organ dysfunction, main acute disease, chronic comorbidities, medications, nutritional needs, and fluid status could better select the right patient, the right time, the right method and, more completely, the right therapeutic bundle. Moreover, the attempt to standardize the timing for RRT into early and delayed, without evaluating each patient with a "holistic" view may expose the patient to both risks of a delayed and an early strategy: in one case being too late and in the other being useless. Great attention, furthermore, should be payed to patients who would recover renal function with conservative treatment alone because those have probably a high chance of good outcome. In conclusion, rather than trying to aprioristically deliver RRT soon or late on the basis of limited scoring systems, it would be better to personalize this vital therapy not differently from all the other therapies commonly administered in critically ill patients with organ failure. These considerations are in agreement with an interesting contribution by Mehta who commented Gaudry *et al.*'s study underlining the "*need for dynamic risk-stratification tools to identify patients who will not need renal-replacement therapy for management of their acute kidney injury*" and that "*meanwhile, we should focus on the timely application of renal-replacement therapy while considering individual patient characteristics, process-of-care elements, and logistics to achieve therapeutic goals*" (6). It is our personal expectation that

further stratification by novel biomarkers and further in depth analysis of patients genotypes might help clinicians in correct therapeutic identification (7,8). As a final thought, however, we would like to remark that, so far, our everyday challenge remains a "phenotypic" and imprecise clinical evaluation, as important and careful, though, as it represents the cornerstone of patients' survival. It is possible that the Standard *vs.* Accelerated Initiation of RRT in Acute Kidney Injury (STARRT-AKI) multicenter trial (NCT02568722), currently recruiting patients (up to a target of about 3,000), will provide us with some more (definitive) iron in the fire.

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Footnote

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Comment on: 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.
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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Supplementary

Table S1 Comparison of Zarbock *et al.*'s and Gaudry *et al.*'s study

	Zarbock *et al*. (*JAMA*)	Gaudry *et al*. (*NEJM*)
Primary outcome	90-day all-cause mortality	Survival at day 60
Secondary outcomes	28- and 60-day mortality, clinical evidence of organ dysfunction, recovery of renal function, requirement of RRT after day 90, duration of renal support, ICU and hospital LoS, and markers of inflammation [IL-6, IL-8, IL-10, IL-18, and macrophage migration inhibitory factor (MIF)]	Receipt of RRT at least once with the delayed strategy; the numbers of RRT-free days, dialysis catheter-free days, MV-free days, and vasopressor therapy-free days SOFA score at day 3 and day 7; the vital status at day 28; the LoS in the ICU and in the hospital; the proportion of patients with treatment limitations (i.e., withholding or withdrawal of treatment); the occurrence of nosocomial infections; and complications potentially related to AKI or RRT
Design	Single-center (University hospital in Germany) randomized clinical trial—August 2013–June 2015	Unblinded, multicenter (31 ICUs in France), randomized trial—September 2013–January 2016
Setting	Early: within 8 hours of diagnosis of KDIGO stage 2	Early: immediately after randomization (KDIGO stage 3+ MV, or catecholamines, or both)*
Participants	Delayed: within 12 hours of diagnosis of KDIGO stage 3 or no initiation	Delayed: if one of the following: (I) severe hyperkalemia (II) metabolic acidosis (III) pulmonary edema (IV) BUN >112 mg/dL (V) Anuria or oliguria >72 hours after randomization
Results	Patients Total: 231 Early: 112 Delayed: 119 Received RRT** Early: 112 (100%) Delayed: 108 (91%) Timing (RRT start) Early: 6.0 hours (Q1, Q3: 4.0, 7.0) Delayed: 25.5 hours (Q1, Q3: 18.8, 40.3) Primary outcome Mortality 90 days Early: 39.3%; Delayed:54.7%; P=0.03 Secondary outcomes Duration of RRT (I) Early: 9 days (Q1, Q3: 4, 44) for the early group; (II) Delayed: 25 days (Q1, Q3: 7, >90); (III) P=0.04; (IV) Between-group difference, –18 Enhanced recovery of renal function at day 90 (I) Early: 53.6%; (II) Delayed: 38.7%; (III) P=0.02 (IV) Between-group difference, 14.9% MV (I) Early: 125.5 hours (Q1, Q3: 41, 203); (II) Delayed: 81.0 days (Q1, Q3: 65, 413); (III) P=0.002; (IV) Between-group difference, –60 hours LoS (hospital) (I) Early: 51 days (Q1, Q3: 31, 74); (II) Delayed 82 days (Q1, Q3: 67, >90) for the delayed group; (III) P<0.001 LoS (ICU) (I) Early: 19 days (Q1, Q3: 9, 29); (II) Delayed: 22 days (Q1, Q3: 12, 36) in the delayed group; (III) P=0.33; (IV) Between-group difference, –3.0 Requirement of RRT on day 90 (I) Early: 13.4%; (II) Delayed: 15.1%; (III) P=0.80 CK (IL-6) (I) Early: 399.4 pg/mL; (II) Delayed: 989.3 pg/mL; (III) P=0.02 CK (IL-8) (I) Early: 65.7 pg/mL; (II) Delayed: 215.5 pg/mL; (III) P=0.001 MIF, IL-10, and IL-18 did not differ between groups	Patients Total: 619 Early: 311 Delayed: 308 Received RRT** Early: 305 (98%) Delayed: 157 (51%) Timing (RRT start) Early: median of 2.0 hours (IQR, 1–3) Delayed: median 57 hours (IQR, 25–83) Primary outcome Mortality 90 days Early: 58.5% Delayed: 49.7% P=0.79 Secondary outcomes In the delayed-strategy group, 61% of the 155 who were alive at day 60 had not received RRT Dependence on RRT at day 28 (I) Early: 12%; (II) Delayed: 10%; (III) P=0.51 Dependence on RRT at day 60 (I) Early: 12% (II) Delayed: 10% (III) P=0.12 Catheter-related bloodstream infections (I) Early: 10% (II) Delayed: 5% (III) P=0.03 Hypophosphatemia: (I) Early: 22%; (II) Delayed: 15%; (III) P=0.03 Other secondary outcomes did not differ significantly between the two study groups; adequate diuresis together with no need for RRT were observed earlier in the delayed-strategy group than in the early strategy group (P<0.001)
Conclusions	Among critically ill patients with AKI, early RRT compared with delayed initiation of RRT reduced mortality over the first 90 days	No significant difference with regard to mortality between an early and a delayed strategy for the initiation of RRT. A delayed strategy averted the need for RRT in an appreciable number of patients

*, without life-threatening conditions related to renal failure. AKI compatible with a diagnosis of acute tubular necrosis in the context of ischemic or toxic injury; **, the choice of the method of renal replacement therapy was left to the discretion of each study site; RRT, renal replacement therapy; LoS, length of stay; IL, interleukin; ICU, intensive care unit; AKI, acute kidney injury; MV, mechanical ventilation; SOFA, Sequential Organ Failure Assessment; KDIGO, Kidney Disease Improving Global Outcomes; Q, quartile; IQR, interquartile range.