Dear ladies and gentlemen, dear ADVOS users and interested parties,
we are pleased to present you another issue of our ADVOS Literature Service. We regularly select one or more papers from international journals which might be of interest to you in connection with our ADVOS procedure. This month we have selected the following:

TIMING OF INITIATION OF RENAL REPLACEMENT THERAPY IN ACUTE KIDNEY INJURY.

Key message

An incredible effort has been performed to conduct large randomized clinical trials to determine the timing of initiation of renal replacement therapy (RRT) in critically ill patients with acute kidney injury (AKI). Although it is still being discussed which strategy is more beneficial, the recent studies make clear that:

- AKI occurs in the context of multiple organ failure.
- AKI patients present with high mortality rates irrespective of the timing of RRT.
- Mortality rates are even higher in patients who received RRT once complications such as metabolic acidosis, persistent hyperkalemia or extra-renal organ damage occurred.
- Less than 15% of AKI patients who met the inclusion criteria in the STARRT Study (Standard versus Accelerated Initiation of Renal-Replacement Therapy) were finally included in the study. This makes the outcomes non-generalizable.
- Clear RRT start criteria need to be defined, preferably stratifying patients individually and dynamically into emergency or elective strategies (e.g. persistent acid-base imbalance, positive fluid-balance or extra-renal organ failure), instead of using static definitions (e.g. KDIGO or RIFLE criteria).
- In addition, enrichment strategies could benefit future studies and treatment guidelines. Here, a specific group of patients or a sub-phenotype that could benefit most from the intervention should be selected. (please check Table 2 at the end of the newsletter, and the publications by Seymour or Bhatraju).
- In this regard, patients with multiple organ failure, higher rates of mechanical ventilation, vasopressor need and acid-base balance derangement would benefit from an early strategy.
- In order to reduce the high mortality in this subgroup of patients with multiple organ failure, other approaches able to additionally eliminate other kind of toxins and offering support to other organs are intriguing.

We report here the results of the STARRT-AKI study (Standard versus Accelerated Initiation of Renal-Replacement Therapy in Acute Kidney Injury) and compare these data with previously published similar studies such as the AKIKI, ELAIN and IDEAL-ICU.

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Comparison of the four most important trials dealing with the timing of the initiation of RRT in patients with AKI

	AKIKI (Gaudry)	ELAIN (Zarbock)	IDEAL-ICU (Barbar)	STARRT-AKI (Bagshaw)
Patients, n	620	231	477	2,927
Design & countries	Multi-center (31), France	Single-center, Germany	Multi-center (29), France	Multi-center (168), 15 countries
Setting	80% sepsis	95% surgical	Septic shock	67% medical
SOFA-Score at enrollment	11±3	16±2	12±3	12±4
AKI criteria	KDIGO stage III	KDIGO stage II	RIFLE, SOFA-Score	KDIGO stage II or III
Criteria for early RRT	≤6 h of stage III AKI	≤8 h of stage II AKI & NGAL ≥150 ng/ml	≤12 h stage III AKI	≤12 h of stage II AKI
Criteria for delayed RRT	Urgent criteria[a]	≤12 h of stage III AKI & NGAL ≥150 ng/ml	48 h of stage III AKI	AKI for 72 h or conventional criteria[b]
Primary outcome	60-day mortality	90-day mortality	90-day mortality	90-day mortality
Mortality: early RRT	49%	39%	58%	44%
Mortality: delayed RRT (%)	50%	55%	54%	44%
Patients never receiving RRT in delayed group (%)	49%	9%	38%	38%
Mortality: delayed group NOT on RRT (%)	37%	N/A	N/A	N/A
Mortality: delayed group on RRT (%)	62%	N/A	68%	N/A
Dialysis- dependence at 90 days (%)	2 (early) versus 5 (delayed) at 60 days	13 (early) versus 15 (delayed)	2 (early) versus 3 (delayed)	10.4 (early) versus 6.0 (delayed
Additional findings	Higher rate of catheter-related bloodstream infections in the early RRT group (10% vs. 5%; p=0.03) and hypophosphatemia (22% vs. 15%; p=0.03)	Larger renal recovery at 90 days (54% vs. 39%; p=0.02), shorter duration of RRT (9 days vs. 25 days; p=0.04), shorter hospital length of stay with early RRT (51 days vs. 82 days; p<0.001)	Higher rate of hyperkalemia in the delayed group (0% vs. 4%; p=0.03)	Higher rate of hypotension and hypophosphatemia in the delayed group (8.7% vs. 5.6% delayed; p=0.001) and hypophosphatemia (7.5% vs. 4.2% delayed; p<0.001)
Outcome	No difference	Survival benefit early versus late	No difference	No difference

Table 1. Randomized controlled trials investigating optimal timing of RRT in patients with AKI

[a] Severe hyperkalemia (>6 mmol/l), severe pulmonary edema refractory to diuretics, severe acidosis (pH <7.15), serum urea >40 mmol/l or oligo-anuria >72 h.

[b] Serum potassium level ≥6.0 mmol/l, pH ≤7.20 or serum bicarbonate level ≤12 mmol/l, severe respiratory failure (paO2/FiO2 ≤200) and clinical perception of volume overload. AKI: acute kidney injury; KDIGO: Kidney Disease, Improving Global Outcomes; RIFLE: risk, injury, failure, loss, and end-stage kidney disease; SOFA-Score; Sepsis-related organ failure assessment score; RRT: renal replacement therapy; N/A: not available; NGAL: neutrophil gelatinase- associated lipocalin. Adapted from Bouchard et al. 2020

STARRT-AKI, Bagshaw et al. 2020

Methods

A multinational, randomized, controlled trial involving critically ill patients with severe AKI was performed. Patients were randomly appointed to receive an accelerated strategy of renal replacement therapy (therapy start within 12 hours after the patient had met eligibility criteria) or a standard strategy (in which renal replacement therapy was discouraged unless conventional indications developed or acute kidney injury persisted for >72 hours). Death at 90 days (any cause) was the primary outcome.

Results

- 3,019 patients were randomized.
- 2,927 patients (97%) were included in the modified intention-to-treat analysis (1,465 in the accelerated strategy group and 1,462 in the standard strategy group).
- Renal replacement therapy was performed in 1,418 (96.8%) in the accelerated strategy group and in 903 (61.8%) in the standard strategy group.
- At 90 days, 643 patients (43.9%) in the accelerated strategy group and 639 (43.7%) in the standard strategy group (relative risk, 1.00; 95% confidence interval [CI], 0.93 to 1.09; P = 0.92) had died.
- Surviving the 90 days, 85 of 814 patients (10.4%) in the accelerated strategy group and 49 of 815 patients (6%) in the standard strategy group (relative risk, 1.74; 95% CI, 1.24 to 2.43) continued dependency on renal replacement therapy.
- In 346 of 1,503 patients (23%) in the accelerated strategy group and in 245 of 1,489 patients (16.5%) in the standard strategy group (P<0.001) adverse events appeared.

Strengths according to the authors of the study

1. The ability to detect a clinically important difference in mortality between accelerated and standard initiation of renal replacement therapy was accomplished by the large sample size of about 3,000 patients.
2. Broad generalizability due to a wide spectrum of ICUs in several countries.
3. The trial deliberately enrolled patients for whom the decision on the initiation of renal replacement therapy was genuinely uncertain.

Potential limitations according to the authors of the study

1. By allowing clinicians to use their judgment in confirming full eligibility, they may have introduced patient heterogeneity into the trial. They did not observe any evidence of considerable heterogeneity of treatment outcome through subgroups, including illness severity and geographic region.
2. The protocol provided recommendations on when to start renal replacement therapy in patients in the standard-strategy group. The physicians had some freedom of choice, which might have resulted in variable initiation times.
3. Adverse events were more frequent in the accelerated strategy group. This result might be partly attributed to the prespecified attention on reporting events related to renal replacement therapy and to the larger number of patient days of such therapy with this strategy.

The authors of the study conclude

Among critically ill patients with acute kidney injury, neither the accelerated renal replacement strategy nor the standard strategy was associated with a lower risk of death at 90 days.

AKIKI, Gaudry et al. 2016

In the study by Gaudry et al. published in 2016, critically ill patients with severe AKI KDIGO classification stage III and with no possibly life-threatening complications were assigned to an early or a delayed strategy of renal replacement therapy. They found no significant difference regarding the 60-day mortality comparing an early and a delayed strategy for the initiation of renal replacement therapy. A delayed strategy prevented the need for renal replacement therapy in an appreciable number of patients (49%). The recovery of renal function (marked by diuresis) was more rapid and catheter-related infections occurred less frequently in the delayed-strategy group than in the early-strategy group. Slight or undetected circulatory alterations might have slowed the apparent recovery of renal function in the early-strategy group. The lengths of stay in the ICU and in the hospital were similar, which indicates that allowing time for renal function recovery did not lead to prolongation of the stay in the ICU.

Potential limitations according to the authors of the study

1. The power of the study to differentiate a significant difference in mortality could be questioned. For an effect size of 1.2 percentage points with a power of 90%, a sample of more than 70,000 patients would be required.
2. Although they did not use Kt/V to evaluate the dose of renal replacement therapy, low urea levels in serum were maintained during therapy. (Kt/V is a measure of the clearance of urea in which K represents the rate of urea clearance by the dialyzer, t is the duration of dialysis, and V is the volume of distribution of urea in the patient.)
3. The patients in the trial had advanced AKI, and therefore the results may not be generalizable to patients with different KDIGO stages of AKI.
4. Some could interpret the finding of higher mortality among patients who received late renal replacement therapy as a deleterious effect of this strategy. The patients who received late renal replacement therapy obviously had more severe illness than those who did not, and further adjustment according to baseline severity suggests that this observed crude difference was confounded.

ELAIN, Zarbock et al. 2016

Zarbock et al. reported in 2016 of critically ill patients with AKI KDIGO stage II. Primary end point was mortality at 90 days after randomization. Secondary end points included:

- 28- and 60-day mortality
- clinical evidence of organ dysfunction
- recovery of renal function
- requirement of RRT after day 90
- duration of renal support
- intensive care unit (ICU) and hospital length of stay

Early beginning of RRT significantly reduced the 90-day mortality. More patients in the early group recovered renal function by day 90. Duration of RRT and length of hospital stay were significantly shorter in the early group. No significant effect on requirement of RRT after day 90, organ dysfunction, and length of ICU stay was observed.

Potential limitations according to the authors of the study

1. Although a large mortality difference was detected, this was not a multicenter trial, and as with many single-center studies, the observed effect size is likely inflated.
2. Larger trials are needed because small trials cannot avoid small baseline differences.
3. Another limitation of this study is the limited generalizability, because almost all patients recruited were surgical patients. This study provides important feasibility data for an AKI stage-based, biomarker-guided interventional trial in AKI.

IDEAL-ICU, Barbar et al. 2018

In the trial by Barbar et al. 2018, patients with early-stage septic shock who had severe AKI (failure stage) according to the RIFLE classification system but without life-threatening complications were assessed. The primary outcome was death at 90 days. The trial was stopped early because of futility. No significant differences in the characteristics at baseline were observed. 38% of patients in the delayed-strategy group did not receive renal replacement therapy at all. Criteria for emergency renal replacement therapy were met in 17% of the patients in the delayed-strategy group. Among patients with septic shock who had severe AKI, no significant difference in overall mortality at 90 days was observed.

Potential limitations according to the authors of the study

1. The RIFLE classification was used to identify appropriate patients. At the time the trial was designed, RIFLE was the most commonly used classification for the identification of patients with AKI. Studies have shown that RIFLE is not as sensitive as the most recent classification systems. The RIFLE failure stage was not necessarily proposed to identify patients who would require renal replacement therapy.
2. Choice of a delay of only 48 hours might not be sufficiently long enough to allow recovery of renal function in some patients or to detect a difference between early and delayed initiation of renal replacement therapy. Barbar and his team assumed that a longer delay would be unethical and unsafe for patients who actually needed renal replacement therapy.

Our comment

First, we want to congratulate the authors for the great effort on conducting such well-designed studies. Although high mortality levels are observed, even higher rates could be expected according to the multiple organ involvement and the high SOFA Scores. The results show that the timing of the initiation of a renal replacement therapy in AKI is a long-standing clinical dilemma.

The potential advantage of earlier initiation of dialysis in AKI is that it may improve acid-base, electrolyte, and fluid balance, thereby preventing more severe complications of AKI and enhancing removal of toxins. Some data suggest that RRT before the onset of severe AKI may attenuate kidney-specific and non-kidney organ injury caused by acidemia, uremia, fluid overload, and systemic inflammation which could potentially translate into improved survival and earlier recovery of kidney function. In fact, only in the ELAIN study, where an early intervention was applied on AKI stage II, an improvement on the primary outcome was shown. In contrast, in patients in AKI stage III no difference could be demonstrated between accelerated or delayed intervention. In our opinion, waiting until AKI stage III has developed, where even higher mortality is expected, means already a delayed strategy that results in lower chances of success for interventions. This is clearly shown by the higher mortality (> 60%) in patients in the delayed group that received RRT.

Moreover, in the STARRT Trial only 12.7% of the patients that met the inclusion criteria were finally included. Indeed, many patients had already emergency indications for RRT (hyperkalemia, metabolic acidosis). Thus, the results of the study might not be generalizable.

Instead, rather than using static parameters such as the definition of the AKI stage based on KDIGO or RIFLE criteria, patients should be individually and dynamically stratified based on the risk of death into emergency or elective strategies. Clear endpoints such as metabolic acidosis, positive fluid-balance or distant organ failure may help to decide the initiation of the intervention, irrespective if this falls into an “early” or a “delayed” group.

A criticism of applying the early strategy for RRT initiation in patients who would recover renal function with conservative treatment alone, would be the exposure to a higher potential risk associated with the RRT intervention. This might be true if the selected patients are not appropriate. Therefore, we should try to find different subgroups according to clinical markers and pathophysiological mechanisms that indicate those patients who would benefit more from an early intervention. In this regard, the works by Seymour and Bhatraju found several phenotypes with significant differences in mortality (Table 2). Those with worse outcome had higher rates of multiorgan failure, vasopressor need or mechanical ventilation. It is meaningful to think that these patients may benefit from an early intervention, while phenotypes with better prognosis could fit into a delayed strategy. In critically ill patients belonging to the hepatic phenotype from Seymour or the AKI-SP2 from Bhatraju an early extracorporeal multiple organ approach may result beneficial as it could avoid further organ damage not only in the kidney but in distant organs, such as the liver or the lung by the removal of additional toxins.

ADVOS multi has been used safely in critically ill patients with multi organ failure (MOF). It is an enhanced therapy supporting liver, lung, kidney and acid-base balance correction. The ADVOS therapy can reduce bilirubin levels, remove CO_2, or eliminate H^+ in case of acidosis. This cannot be achieved with conventional renal replacement therapy. An early use of ADVOS multi (e.g. at AKI stage II with either liver dysfunction or acidosis), even in patients with severe prognosis, may gain time to bridge the patient to recovery or to transplantation. Encouraging data already exist, but more studies are needed.

	Seymour 2019		Bhatraju 2019	
Phenotype	ß ("renal")	δ ("hepatic")	AKI-SP1	AKI-SP2
28-day mortality	13%	40%	6%	25%
Kidney	SCr: 2.3 mg/dl	SCr: 1.8 mg/dl	SCr: 1.4 mg/dl	SCr: 3.1 mg/dl
Liver	Bilirubin: 0.6 mg/dl	Bilirubin: 1.4 mg/dl	Cirrhosis: 2%	Cirrhosis: 20%
Lung	RR: 20 MV: 8 days	RR: 25 MV: 8 days	MV: 63%	MV: 83%
Acid-Base	HCO_3^-: 25 mmol/l	HCO_3^-: 20 mmol/l	HCO_3^-: 22 mmol/l	HCO_3^-: 17 mmol/l
Hemodynamic	Lactate: 1.2 mmol/l Vasopressors: 4 days IL-6: 415 pg/ml	Lactate: 3.3 mmol/l Vasopressors: 4 days IL-6: 910 pg/ml	Vasopressors: 14% sTNFR-1: 6,798 pg/dl	Vasopressors: 49% sTNFR-1: 18,772 pg/dl
Coagulation	Platelets: 200 x 10^9/L	Platelets: 164 x 10^9/L	Platelets: 184 x 10^9/L	Platelets: 85 x 10^9/L
SOFA Score	3.5	6.6	3	7
Our suggested strategy for extracorporeal support	Delayed	Early	Delayed	Early

Table 2. Phenotypes in critically ill patients.
SCr: serum creatinine; RR: respiratory rate; MV: mechanical ventilation; HCO_3^-: serum bicarbonate; sTNFR-1: soluble tumor necrosis factor receptor 1.

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