

Timing of Kidney Support Therapy in Acute Kidney Injury: What Are We Waiting For?

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The optimal timing of kidney support therapy in critically ill patients with acute kidney injury (AKI) without life-threatening complications related to AKI is controversial. Recent multicenter, randomized, controlled studies have questioned the need for earlier initiation of therapy, despite one study showing a benefit in survival and others with no differences in mortality based on the timing of kidney support therapy initiation. These findings reflect the uncertainties in decisions to initiate kidney support therapy, which should ideally be individualized according to the patient's comorbidities, severity of illness, trajectory of kidney function, and urine output as well as requirements for fluid balance and solute removal. A delayed approach could translate into a potentially reduced burden of dialysis dependence in addition to saving health resources. However, we must ascertain what constitutes the waiting period and the benefits and risks associated with this approach. This article reviews the concept of timing of dialysis in AKI, performs a critical assessment of the most important clinical trials in this topic, discusses ongoing research and knowledge gaps, and defines key research issues to address in the future.

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Introduction

Acute kidney injury (AKI) is frequent and is associated with an increased risk of chronic kidney disease (CKD),¹ kidney failure,¹ congestive heart failure,² coronary events,^{2,3} sepsis,^{4,5} stroke,² bleeding,^{6,7} and mortality.⁸ The annual incidence of AKI is 2,000-3,000 per million, among whom 200-300 will be treated with dialysis.⁹ Incidence of short-term dialysis is highest in critically ill, septic patients, and those undergoing cardiovascular surgery,⁹ with an increasing trend in the use of dialysis in critically ill patients.¹⁰⁻¹²

In patients with life-threatening indications refractory to medical treatment (eg, hyperkalemia, metabolic acidosis, uremic complications, fluid overload), there is a clear need to initiate dialysis rapidly (Box 1). However, despite these indications there is wide variability in the timing of initiation of dialysis in clinical practice.¹³⁻¹⁶ Dialysis should be viewed as kidney support therapy (KST) because it can remove uremic toxins, correct electrolyte and acid-base disturbances, achieve fluid balance to facilitate the administration of nutrition or drugs, can modulate cytokine levels during inflammatory conditions, and be included in platform of multiorgan support to limit damages related to organ crosstalk. However, these considerations must include exposing the patient to vascular access- and dialysis-associated complications including biocompatibility issues. The ongoing arguments for and against specific timing for KST have contributed to various clinical practice guidelines over the last decade, with inconsistent recommendations, except for urgent indications (Table 1).

Summary of Recent and Ongoing Randomized Controlled Trials

Six randomized controlled trials (RCTs) have been published over the last 5 years to determine the optimal timing of KST initiation (Table 2).¹⁷⁻²¹ Most of these trials defined

early versus delayed approaches for KST start based on AKI severity according to KDIGO staging and AKI-associated complications. The ELAIN study showed a survival benefit with early versus late KST, whereas the AKIKI, IDEAL-ICU, FST, and STARRT-AKI RCTs did not replicate these findings. More recently, the AKIKI2 trial showed that a more delayed approach is associated with worse outcomes.

The ELAIN trial was a single-center RCT of predominantly cardiac surgical patients to determine whether early KST (starting within 8 hours of KDIGO stage 2 AKI) would improve patient survival compared with delayed KST initiated for an urgent indication or within 12 hours of stage 3 AKI (Table 2).²⁰ A plasma neutrophil gelatinase-associated lipocalin (NGAL) above 150 ng/mL was required, as well as one of the following: severe sepsis, use of vasopressors, refractory fluid overload (defined as worsening pulmonary edema, $\text{PaO}_2/\text{FiO}_2 < 300$ mm Hg or fluid balance $> 10\%$ of body weight), or development/progression of nonrenal organ dysfunction (Sequential Organ Failure Assessment [SOFA] score ≥ 2). The trial included 231 patients with a mean SOFA score of 16. All patients in the early group received KST compared with 91% of patients in the delayed group. The early KST intervention showed a 15% absolute reduction in 90-day mortality (39% vs 55%; $P = 0.03$) and a greater renal recovery at 90 days (54% vs 39%, $P = 0.02$). Of note, the ELAIN trial had a Fragility Index of 3, meaning that a shift of 3 more deaths in the early group or 3 fewer deaths in the delayed group would have modified the outcome into a nonsignificant result. It is common that results from single-center RCTs are discrepant from those of subsequent multicenter RCTs.²² Single-center RCTs are known to report larger treatment effects than multicenter RCTs²³ and have more limited external validity.²² The addition of NGAL as an inclusion criterion excluded only 3 out of 373 eligible patients for having plasma NGAL of < 150 ng/mL.

Box 1. Factors to Consider for KST Initiation in AKI**Absolute indications**

- Symptoms or signs attributable to uremia (pericarditis, encephalopathy)
- Refractory pulmonary edema (diuretic resistant)
- Refractory hyperkalemia (potassium > 6.5 mmol/L or rapidly increasing, or associated with cardiac arrhythmias)
- Refractory metabolic acidosis (pH < 7.2)

Relative indications

- Presence or anticipation of relevant organ dysfunction impacted by AKI/fluid overload
- Need for large volume fluid administration (ie, nutritional support, drugs, or blood products)
- Solute burden (ie, tumor lysis syndrome, rhabdomyolysis, intravascular hemolysis)
- Unfavorable evolution of clinical parameters/severe AKI or oligoanuria with low probability of rapid renal recovery

Relative contraindications

- Futility considering the global prognosis (palliative care, limited survival regardless of KST)
- High likelihood of dialysis dependence if long-term dialysis is unacceptable

Risks of KST

- Complications related to vascular access, including the risk of catheter infection and thrombosis
- Bleeding or heparin-induced thrombocytopenia related to anticoagulation
- Hemodynamic instability and potential risk of worsening long-term kidney function
- Clearance of drugs/water-soluble vitamins/trace elements/electrolytes
- Biocompatibility issues
- Immobilization favoring muscle wasting and thrombotic events, and limiting physiotherapy

Other factors

- Availability of equipment and personnel
- Patient and family preferences/overall goals of care
- Health care costs

Abbreviations: AKI, acute kidney injury; KST, kidney support therapy.

The first large multicenter RCT, the AKIKI trial, included 620 critically ill predominantly septic patients receiving mechanical ventilation and/or vasoactive support in 31 centers in France (Table 2).¹⁹ The average SOFA score was 11 ± 3. In comparison with ELAIN, the early group was not as prompt to receive KST, the criterion being initiation of KST within 6 hours of fulfilling AKI stage 3. In the late group, KST was initiated only when urgent indications were met. The trial was designed to detect a 15% absolute reduction in mortality in critically ill patients, which is very rarely seen in modern clinical practice with a single intervention. Mortality at 60 days was similar: 49% in early treatment group versus 50% in the late treatment group. Of note, 49% of patients in the late group never received KST. Dialysis dependence at 60 days was similar between the groups.

The IDEAL-ICU RCT, a 29-site study in France, enrolled 477 critically ill patients with early septic shock and AKI

(Table 2).¹⁷ Early KST was defined as KST initiation within 12 hours of KDIGO stage 3 AKI, whereas delayed KST was defined as KST deferred for at least 48 hours from KDIGO stage 3 AKI, unless absolute indications occur. The mean SOFA score was 12 ± 3. The primary end point, 90-day mortality, was comparable between the early (58%) and late (54%) groups at a planned interim analysis, and the study was stopped due to futility. Once again, a large percentage of patients in the late group never received KST (38%), among whom 8% died before KST and 29% recovered sufficient kidney function to avoid KST.

More recently, the STARRT-AKI enrolled over 2,900 critically ill patients in 15 countries with AKI KDIGO stage 2 AKI or higher (Table 2).²¹ The study compared an early strategy (KST within 12 hours after eligibility criteria were met) with a standard approach where KST was postponed unless AKI lasted for at least 72 hours or traditional indications occurred (serum potassium ≥ 6.0 mmol/L, pH ≤ 7.20, or a serum bicarbonate ≤ 12 mmol/L, severe respiratory failure defined as Pao₂/Fio₂ ratio ≤ 200, and clinical perception of volume overload). The aim was to demonstrate an absolute 6% improvement in 90-day survival.²¹ Key secondary outcomes included dialysis dependence; a composite of death or dialysis dependence; and major adverse kidney event (MAKE) at 90 days. Patients with advanced CKD (estimated glomerular filtration rate [eGFR] < 20 mL/min/1.73 m²), those with uncommon causes of AKI, those who needed emergent dialysis, or kidney transplant recipients were excluded. Patients for whom the attending physicians considered that urgent KST was required or KST should be deferred were also excluded. As a result, 67% of the 11,852 eligible patients were excluded, leaving 3,019 enrolled patients, among whom 2,927 were included in the modified intention-to-treat analysis. It is unclear whether the characteristics of the enrolled patients differed from the excluded patients for whom KST was immediately initiated or could be deferred.

For STARRT-AKI, the mean SOFA score was 12 ± 4, 45% were oligoanuric, and the percentage of fluid overload adjusted for body weight (%FO) was 3%. Similar to other trials, 38% of patients in the late group never received KST. The time from eligibility to KST initiation was 6 hours in the early treatment group compared with 31 hours in the late treatment group. Two-thirds of the patients dialyzed in the late group were initiated due to a conventional indication, 24% for AKI lasting more than 72 hours, and 10% for unclear reasons. The primary outcome, 90-day mortality, was equal in both groups (44%). Serious adverse events were reported in 0.8% of patients. More adverse events were reported in the early group (23% vs 17%; relative risk [RR], 1.40 [95% CI, 1.21-1.62]) mostly due to KST-related hypotension (8.7% early vs 5.6% late) and hypophosphatemia (7.5% early vs 4.2% late). Dialysis dependence was higher at 90 days in the early group (10.4% vs 6.0%; RR, 1.74 [95% CI, 1.24-2.43]), and the risk of rehospitalization was also increased in this

Table 1. Summary of Clinical Practice Guidelines for Starting KST in Critically Ill Patients With AKI

Organization	Year	Recommendations
Kidney Disease: Improving Global Outcomes (KDIGO) AKI guideline ⁴⁴	2012	Initiate KST emergently when life-threatening changes in fluid, electrolyte, and acid-base balance exist. (<i>Not Graded</i>) Consider the broader clinical context, the presence of conditions that can be modified with [KST], and trends of laboratory tests—rather than single [S]UN and creatinine thresholds alone—when making the decision to start [KST]. (<i>Not Graded</i>)
French Intensive Care Society (SRLF) ⁴⁵	2015	[KST] should be initiated without delay in life-threatening situations (hyperkalemia, metabolic acidosis, tumor lysis syndrome, refractory pulmonary edema). (<i>Expert Opinion; Strong Agreement</i>) The available data are insufficient to define optimal timing of [KST] initiation outside life-threatening situations. (<i>Expert Opinion; Strong Agreement</i>) In children, fluid and sodium overload probably > 10%, and very probably > 20%, should be considered as one of the criteria for initiation of [KST]. (<i>Expert Opinion; Poor Agreement</i>) “Early” initiation of [KST] means at KDIGO stage 2 or within 24 hours after acute renal failure of which reversibility seems unlikely. (<i>Expert Opinion; Poor Agreement</i>) “Late” initiation of [KST] means > 48 hours after onset of acute renal failure, KDIGO stage 3, or when a life-threatening situation arises because of acute renal failure. (<i>Expert Opinion; Poor Agreement</i>)
Acute Dialysis Quality Initiative (ADQI) ⁴³	2016	[Short-term KST] should be considered when metabolic and fluid demands exceed total kidney capacity. Demand for kidney function is determined by nonrenal comorbidities, the severity of the acute disease and solute and fluid burden. The demand-capacity imbalance is dynamic and should be evaluated regularly.
National Institute for Health and Care Excellence (NICE) ⁴⁶	2019	Discuss any potential indications for [KST] with a nephrologist, pediatric nephrologist, and/or critical care specialist immediately to ensure that the therapy is started as soon as needed. Refer adults, children, and young people immediately for [KST] if any of the following are not responding to medical management: hyperkalemia, metabolic acidosis, symptoms or complications of uremia (for example, pericarditis or encephalopathy), fluid overload, pulmonary edema. Base the decision to start [KST] on the condition of the adult, child, or young person as a whole and not on an isolated urea, creatinine, or potassium value.
KDIGO Controversies in AKI ⁴⁷	2020	Optimal timing for [short-term KST] remains unknown. ... [KST initiation] should be considered when metabolic and fluid demands exceed the kidney's capacity. ... This concept acknowledges the dynamic nature of acute illness and stresses the importance of regular evaluation of the demand and renal capacity relationship. However, the exact methods for determining demand and capacity are unknown. ... Use of a standardized FST can be considered in AKI, to further quantify the likelihood of AKI progression, and integrated into the spectrum of clinical information available when planning for and deciding to initiate [KST]. Risk of complications, global prognosis, potential for recovery, and patient preferences should be considered when taking the decision.
Society of Critical Care Medicine Guidelines in Acute or Acute on Chronic Liver Failure ⁴⁸	2020	We suggest using [KST] early in patients with ALF and AKI. (<i>Very Low Quality of Evidence</i>)

Except as indicated, statements are quoted from the listed sources. Abbreviations: ALF, acute liver failure; FST: furosemide stress test; KST: kidney support therapy; SUN, serum urea nitrogen; TLS, tumor lysis syndrome.

group (RR, 1.23 [95% CI, 1.02-1.49]). A meta-analysis published before STARRT-AKI also found a higher risk of hypotension with early KST.²⁴

The FST trial was a multicenter pilot study to determine (1) whether FST could be useful as a screening tool for patients at high risk for KST, and (2) the feasibility of using FST in a trial on timing of KST.¹⁸ By definition, the FST consists of 1 mg/kg of intravenous furosemide to furosemide-naïve patients and 1.5 mg/kg to previous users.²⁵ Nonresponsive patients were defined as having urine output less than 200 mL in 2 hours. In the FST trial, 118 nonresponsive patients were randomized to early treatment, initiation within 6 hours, or standard KST. In the early group, 98% received KST compared with 75% in

the standard group. There were no differences in 28-day mortality (62% vs 58%, $P = 0.68$), or 28-day KST dependence.

Finally, the multicenter AKIKI-2 RCT further evaluated the effect of increasing the time to initiate KST from that tested in the AKIKI trial. They enrolled 278 patients in France who were randomized to KST initiation within 12 hours of urea > 40 mmol/L and/or oligoanuria for >72 hours, or a delayed strategy where KST was initiated if one or more of these criteria occurred: urea > 50 mmol/L, noticeable hyperkalemia or acidosis, or refractory pulmonary edema due to fluid overload resulting in severe hypoxemia.²⁶ The primary outcome, the number of KST-free days at 28 days after randomization, was similar

Table 2. Comparison Between Recent Large Randomized Controlled Trials on Optimal Timing of KST in AKI

	ELAIN	AKIKI	IDEAL-ICU	FST	STARRT-AKI	AKIKI2
No. of patients	231	620	477	118	2,927	278
Design and countries	Single-center, Germany	Multicenter (31), France	Multicenter (29), France	Multicenter, Thailand	Multicenter (168), 15 countries	Multicenter (39), France
Recruitment period	2013-2015	2013-2016	2012-2016	2016-2017	2015-2019	2018-2019
Mean age, y	67	66	69	67	65	65
Male sex	63%	66%	61%	49%	68%	74%
Setting	95% surgical (mostly cardiac and abdominal)	80% sepsis	Septic shock	Mixed, 68% medical	67% medical	Received mechanical ventilation and/or vasopressors; 58% septic shock
Exclusion	CKD stage 4-5, prior KST, KTx, or uncommon causes of AKI	Urgent criteria for KST	Urgent criteria for KST	Baseline Scr ≥ 2 (M), ≥ 1.5 (F) mg/dL, KTx, pregnancy, allergy to loop diuretics, expected death in 24 h or low chance of survival to 28 d, DNR, KST in prior 30 d, sAlb < 2 g/dL, ECMO	Urgent criteria for KST, prior KST, advanced CKD (GFR < 20 mL/min/1.73 m ²), KTx, uncommon causes of AKI	Urgent criteria for KST, patients with inclusion criteria already present for >24 h, CKD stage 4-5, prior KST, KTx, uncommon causes of AKI, Child C liver cirrhosis, pregnancy
CKD	41%	10%	16%	NA	44%	12%
KST modality	CVVHDF 30 mL/kg/h with citrate with transition to SLEDD or IHD	Physician discretion (IHD and CRRT by center [randomized by center])	Physician discretion (IHD and CRRT by center [randomized by center])	CVVH	Physician discretion (IHD and CRRT by center [randomized by center])	Physician discretion (IHD and CRRT, center as a random effect)
Criteria for early KST	Within 8 h of stage 2 and NGAL ≥ 150 ng/mL	Within 6 h of stage 3	Within 12 h of stage 3	Any AKI with absence of response to FST	Within 12 h of stage 2	Stage 3 and oliguria for 72 h or SUN > 112 mg/dL
Criteria for late KST	Within 12 h of stage 3 and NGAL ≥ 150 ng/mL	Urgent criteria: severe hyperkalemia (>6 mmol/L), severe pulmonary edema refractory to diuretics, severe acidosis (pH < 7.15), serum urea > 40 mmol/L, oligoanuria > 72 h	48 h of stage 3	No response to FST and serum urea > 100 mg/dL; severe hyperkalemia (>6 mmol/L), severe metabolic acidosis (pH < 7.15); severe pulmonary edema	AKI for 72 h or conventional criteria: serum K ⁺ ≥ 6.0 mmol/L, pH ≤ 7.20 , or serum HCO ₃ ≤ 12 mmol/L, severe respiratory failure (PaO ₂ /FiO ₂ ≤ 200), and clinical perception of volume overload	Mandatory indication (noticeable hyperkalemia or metabolic acidosis or pulmonary edema) or until SUN ≥ 140 mg/dL
Blinded analysis	No	No	No	No	No	No
Clinical equipoise	No	No	No	No	Yes ^a	No

(Continued)

Table 2 (Cont'd). Comparison Between Recent Large Randomized Controlled Trials on Optimal Timing of KST in AKI

	ELAIN	AKIKI	IDEAL-ICU	FST	STARRT-AKI	AKIKI2
Absolute risk reduction target	18%	15%	10%	NA (pilot study)	6%	NA (not the same primary outcome)
SOFA score at enrollment	16 ± 2	11 ± 3	12 ± 3	12 ± 4	12 ± 4	12 ± 4
Scr at randomization, mg/dL	2.0 (early) vs 2.0 (late)	3.2 (early) vs 3.2 (late)	3.2 (early) vs 3.4 (late)	2 (early) vs 2.5 (late)	3.6 ± 1.7 (early) vs 3.4 ± 1.6 (late)	5.0 ± 2.0 (early) vs 5.9 ± 2.2 (late)
Oliguria or anuria at randomization	69%	64%	69%	All FST non-responsive	45%	NA
Cumulative fluid balance at randomization and subsequently	6.8 L (early) vs 6.3 L (late); at 3 d: similar between groups	NA	3.2 L/d (early) vs 3.2 L/d (late); at 7 d: similar between groups (5.6 vs 5.9 L)	4.8 L (early) vs 5.1 L (late); at 7 d: -1.7 vs -1.2 L	2.6 L (early) vs 2.8 L (late); later timepoint NA	At 2 d: 1.6 L (early) vs 1.6 L (late); at 7 d: 1.7 vs 2.1 L
Scr at KST initiation, mg/dL	1.9 (early) vs 2.4 (late)	3.3 (early) vs 5.3 (late)	3.2 (early) vs 4.6 (late)	NA	3.7 (early) vs 4.9 (late)	4.8 (early) vs 6.2 (late)
Cumulative fluid balance at KST initiation	NA	NA	NA	4.8 L (early) vs 8.7 L (late)	2.7 L (early) vs 5.9 L (late)	NA
SOFA score at KST initiation	NA	NA	12 ± 3 (early) vs 13 ± 4 (late)	NA	11 ± 4 (early) vs 12 ± 4 (late)	NA
Time difference: early vs late KST	20 h (6 vs 26 h)	55 h (2 vs 57 h)	44 h (8 vs 52 h)	19 h (2 vs 21 h)	25 h (6 vs 31 h)	30 h (3 vs 33 h)
Primary outcome	90-d mortality: 39% (early) vs 55% (late); <i>P</i> = 0.03	60-d mortality: 49% (early) vs 50% (late)	90-d mortality: 58% (early) vs 54% (late)	28-d mortality: 62% (early) vs 58% (late)	90-d mortality: 44% (early) vs 44% (late)	28-d no. of days alive and KST-free: 12 (0-25) for each group ^b
Mortality rate in patients on KST in late group	NA	62%	68%	NA	NA	NA
Patients never receiving KST (delayed group)	9.2%	49%	38%	25%	38%	21%
Dialysis dependence	13% (early) vs 15% (late) at 90 d	2% (early) vs 5% (late) at 60 d	2% (early) vs 3% (late)	12% (early) vs 17% (late) at 28 d	10.4% (early) vs 6.0% (late); RR, 1.74 (95% CI, 1.24-2.43)	3% (early) vs 1% (late) at 60 d
Time on KST per ITT, early vs late	9 (4-44) vs 25 (7-, >90) d	3 (2-7) vs 4 (2-8) sessions	4 (2-8) vs 2 (0-6) d, <i>P</i> < 0.001	NA	4 (2-8) vs 5 (3-9) d ^c	NA
ICU LOS days, early vs late	19 (9-29) vs 22 (12-, 36)	Survivors: 13 (8-23) vs 13 (7-23); nonsurvivors: 6 (2-14) vs 6 (2-13)	11 (4-19) vs 10 (5-19)	12 (7-26) vs 13.5 (9-29)	Survivors: 9 (5-16) vs 10 (5-19) ^e ; nonsurvivors: 7 (3-13) vs 7 (4-15) ^e	18 (12-31) vs 16 (10-32)

(Continued)

Table 2 (Cont'd). Comparison Between Recent Large Randomized Controlled Trials on Optimal Timing of KST in AKI

	ELAIN	AKIKI	IDEAL-ICU	FST	STARRT-AKI	AKIKI2
Additional findings	In early group, greater renal recovery at 90 d (54% vs 39%, $P = 0.02$), shorter KST duration (9 vs 25 d, $P = 0.04$), and shorter LOS (51 vs 82 d, $P < 0.001$)	In early group, higher rates of CRBSI (10% vs 5%, $P = 0.03$) and hypophosphatemia (22% vs 15%, $P = 0.03$)	Higher rate of hyperkalemia in delayed group (0% vs 4%, $P = 0.03$)	FST predicted need for KST: 75% of nonresponders required dialysis in late group; 86% of responders who were not enrolled in the trial avoided KST	In early group, higher rates of hypotension and hypophosphatemia (8.7% vs 5.6%, $P = 0.001$) and hypophosphatemia (7.5% vs 4.2%, $P < 0.001$)	Similar complications between groups, similar CRBSI (13% vs 11%)

Adapted from Bouchard and Mehta⁴⁹ with permission of the copyright holders; original table ©2020 Bouchard and Mehta. Abbreviations: AKI, acute kidney injury; AKIKI, Artificial Kidney Initiation in Kidney Injury; CKD, chronic kidney disease; CRBSI, catheter-related bloodstream infection; CRRT, continuous renal replacement therapy; CVVH, continuous veno-venous hemofiltration; CVVHDF, continuous venovenous hemodiafiltration; DNR, do not resuscitate (advance directive); ECMO, extracorporeal membrane oxygenation; ELAIN, Early Versus Late Initiation of KST in Critically Ill Patients With AKI; F, female; FST, furosemide stress test; GFR, glomerular filtration rate; HCO₃, bicarbonate; ICU, intensive care unit; IDEAL-ICU, Initiation of Dialysis Early Versus Delayed in the Intensive Care Unit; IHD, intermittent hemodialysis; ITT, intention to treat; K⁺, potassium; KDIGO, Kidney Disease: Improving Global Outcomes; KST, kidney support therapy; KTx, kidney transplant; LOS, (hospital) length of stay; M, male; NA, not available; NGAL, neutrophil gelatinase-associated lipocalin; Pao₂/Fio₂, partial pressure of arterial oxygen to the fraction of inspired oxygen; RR, relative risk; sAlb, serum albumin; Scr, serum creatinine; SLEDD, sustained low efficiency dialysis; SOFA, Sequential Organ Failure Assessment; STARRT-AKI, Standard versus Accelerated Initiation of Renal-Replacement Therapy in Acute Kidney Injury; SUN, serum urea nitrogen.

^aCriteria for clinical equipoise: patients were excluded (but could be rescreened for eligibility, if applicable) if either of the following was true. (1) Clinician(s) caring for patient believed that immediate KST was mandated. After fulfilling the inclusion/exclusion criteria, the study team was to speak to the ICU and/or nephrology attending physician and ask if he/she agreed that KST must be initiated immediately for this patient. (2) Clinician(s) caring for patient believed that deferral of KST was mandated. After fulfilling the inclusion/exclusion criteria, the study team was to speak to the ICU and/or nephrology attending physician and ask if he/she agreed that KST must be deferred for this patient. ^b60-day mortality was 44% (early) vs 55% (late).

^cStatistically significant.

between the groups despite fewer patients receiving KST in the delayed group. Crude mortality did not differ between the groups. However, a prespecified multivariate analysis showed that 60-day mortality was higher in the delayed strategy despite a similar rate of complications or length of stay. These results do not imply that a serum urea nitrogen >50 mmol/L is the causal link for increased mortality.

What Can We Learn From These RCTs?

Most studies have defined the timing of KST initiation based on AKI stage, including changes in serum creatinine with or without urine output, timing relative to the development of AKI, or conventional indications for KST (Table 2).^{17,19-21} However, this traditional concept of timing of KST initiation may need to be revised in light of results from recent trials.^{17,19,21} Fluid overload is often a major factor for initiating KST; however, the percentages of fluid overload adjusted for body weight (3% vs 7% in STARRT-AKI) are much lower than previous results from observational studies (where they could reach 20%).²⁷ These findings may reflect an evolution of clinical practice throughout the years after publications from observational studies, as for the %aFO. In the STARRT-AKI, waiting to start KST until the %aFO reaches 7% was not more harmful than initiating KST at a %FO of 3%. Patients with severe %FO may have been excluded from the study. We must not conclude based on these findings that waiting until the %FO reaches 20% is acceptable. Because kidneys are encapsulated organs, they are more likely to suffer from organ congestion and fluid overload. Patients undergoing cardiac surgery or suffering from congestive heart failure may represent clinical phenotypes of patients who could benefit more than others from early renal support and optimized fluid management. Subgroup analyses from previous RCTs including cardiac surgery and congestive heart failure patients could clarify these questions.

Some patients from the ELAIN, AKIKI, or IDEAL-ICU trials may not have been considered to benefit from KST in clinical practice. Results from STARRT-AKI highlighted the absence of tools to predict the need for, or the avoidance of, KST in severe AKI in patients with clinical equipoise. Clinical equipoise was used to guide eligibility rather than time intervals after which patients met the criteria for severe AKI. The use of clinical equipoise excludes patients judged by clinicians as being appropriate candidates for emergency KST or likely to have imminent recovery of kidney function (Table 2). In the STARRT-AKI RCT, a third of eligible patients were deemed uncertain to benefit from KST and were then enrolled after obtaining consent. In the late arm, 25% of patients had to start therapy within 19 hours, and 24% could be deferred to up to 72 hours, or even longer. These findings suggest that a more dynamic approach is needed to quantify the need for KST versus the risks of waiting and those associated with KST on a daily basis. Medical critically ill patients, whose

prognosis relies more on underlying conditions such as septic shock, may not benefit as much from early KST, as shown in subgroup analyses in septic patients from the STARRT-AKI and a previous meta-analysis.^{21,28}

A meta-analysis by Gaudry et al²⁸ published just before STARRT-AKI reported that delayed start was associated with no differences in mortality and these results were unchanged in a sensitivity analysis of different subgroups (age, sex, severity of illness, sepsis, and CKD). These findings suggest that deferring KST whenever possible may lead to a substantial reduction in the percentage of patients who will ultimately receive KST. However, there is a need to better understand why these patients could avoid KST. These reasons were not fully explained in any of the trials. In the STARRT-AKI trial, the authors reported that death occurred in 12.5% of patients before KST. It would be instructive to learn the characteristics and outcomes of patients not receiving KST to guide physicians and improve patient management. For instance, whether there was a difference in urine output and %FO in patients from the late group who received or did not receive KST, and whether a diuretic challenge such as the FST could predict this need. This may also include baseline characteristics as well as the course of kidney function and overall status. The results of the BICAR-ICU RCT suggest that bicarbonate administration can avoid KST in patients with severe metabolic acidosis and AKI, in addition to optimizing outcomes.²⁹ It is unknown whether these findings were applied in recent RCTs.

Long-term kidney function after KST is an important consideration to assess the outcomes of the therapy. Observational trials have found that underlying CKD, incomplete renal recovery, or presence of proteinuria can predict worse kidney outcomes.³⁰ The STARRT-AKI trial included significantly more patients with CKD than previous studies (44% compared with 10% in the AKIKI trial and 16% in the IDEAL-ICU) (Table 2). In a meta-analysis published before this RCT, no significant between-group differences regarding KST dependence were found at hospital discharge, nor in serum creatinine level at the same time point.²⁸ However, the quality of evidence was low. In a meta-analysis including STARRT-AKI, early initiation of KST increased the risk of dialysis dependence in the subgroups of patients not treated with continuous dialysis and whose SOFA score were higher than 11.³¹ Of note, the included studies were highly heterogeneous and subject to biases.

Information on the causes of death in patients not receiving KST would help in determining whether these could have been modified by the provision of KST. For example, oligoanuria and higher %FO at KST initiation have been associated with worse outcomes in observational studies.^{32,33} In STARRT-AKI, median urine output was lower (350 vs 453 mL) and fluid overload more common (6.7% vs 3.1%) at KST initiation in the late group compared with the early group, but these findings did not modify the overall outcomes.

Although waiting for dialysis has been associated with a lower rate of KST, the patients had a longer time on KST and a prolonged intensive care unit length of stay.²¹ Additionally, these patients required significantly higher use of diuretics and drugs to manage fluid overload, hyperkalemia, and acidosis.¹⁹ Sodium polystyrene sulfonate is often used to treat hyperkalemia in the absence of alternative treatments. However, there is concern that this drug promotes intestinal necrosis, especially in post-operative patients and those with ileus, obstruction, or bowel disease. In addition, the influence of drug utilization on overall resource allocation has not been described.

How Should We Update Current Guidelines?

A key issue for the optimal timing of KST is balancing the risk of an unnecessary procedure and need for a vascular access with the possibility of not addressing a potentially treatable condition over time. These concepts are variably considered in these trials as they focused to determine the harm for early start related to complications of therapy and effects on outcomes. However, there is an equally important need to consider the risk of prolonged waiting because delays in starting could result in irreversible disease unlikely to benefit from KST.

We have previously shown that delays in addressing severe AKI result in increased risk of organ failure and fluid overload that are associated with higher mortality.³⁴ Results from the AKIKI2 trial also support these findings. Additionally, complications related to underlying severity of disease have been shown to correspond to a higher attributable risk to mortality.³⁵ Consequently, we need to have specific criteria to determine the outer limits for waiting aimed at delayed intervention.

For patients with urgent KST indications, the anticipated benefits most often surpass the potential risks if correlated with patients' wishes and global prognosis (Fig 1). For patients with relative indications for initiating KST, a clear assessment of the anticipated benefits versus potential risks should be performed, and the patient's or family's care preferences must be considered in the decision. These should be part of shared decision making with the patient and their surrogates when deciding whether KST should be initiated, especially before urgent indications are met. RCTs on timing of KST included intermittent hemodialysis and continuous renal replacement therapy only (Table 2). In the recent COVID-19 pandemic, some centers relied on urgent-start peritoneal dialysis to save lives due to resource constraints.³⁶ Consequently, logistic considerations, such as availability of staff, machines, and disposables, should also be incorporated in the decision-making process.

What's Next?

We must reconsider our approach to studying the timing of KST, which has been driven largely by the severity of

AKI based on serum creatinine criteria and oliguria conditioned by the presence of complications. The recent ADQI recommendations on AKI biomarkers highlighted the need for further research on dynamic assessment of kidney damage and functional biomarkers correlated with clinical data to define the optimal timing of KST.³⁷ If the objective becomes to safely postpone KST as long as possible with “watchful waiting,” there needs to be a clear understanding of the parameters used for defining the waiting period, its duration, and the best approach to implement targeted therapies to manage complications of hyperkalemia, acidosis, and fluid overload. The number and duration of complications are associated with adverse outcomes,^{34,35} so we must refine the risks associated with the waiting period to individualize patient management.

Dynamic, quantifiable measurements are needed to characterize an individual patient’s trajectory. Small studies have found that for most patients FST can predict who is likely to progress to more severe AKI and require KST.^{18,25} In the FST trial, 86% of patients who responded to the test avoided KST, while 75% of nonresponders ultimately required KST.¹⁸ In another study, in early AKI, the FST outperformed common AKI biomarkers to predict the need for KST.²⁵ Machine-learning techniques have also been applied to predict AKI. To our knowledge, 4 models have been developed to predict the need for KST.³⁸⁻⁴¹ The time period used to assess the models ranged from the next 48 hours to the total duration of admission, with good prediction (area under the curve values of 0.82-0.96). These models should be prospectively validated in other cohorts.

Another approach that is currently being evaluated is the computation of the mismatch between the demand placed on kidneys and their capacity.^{42,43} This approach includes the assessment of severity of illness, fluid balance,

as well as AKI severity and urine output at given time points, and provides a dynamic score that trends a patient’s course. Clinicians can individualize treatment according to the trends in the mismatch score and distinguish which patients may be more or less likely to need and benefit from KST. Clinicians may opt to start KST if there is progressive increased demand and reduced capacity, or pursue the waiting approach in patients with improvement in illness severity and kidney function. This integrated approach enhances current clinical practice, where KST is often based on expected trends in fluid balance and illness severity along with worsening AKI and decreasing urine output. Patients’ comorbidities may also be considered, as well as risks and potential harms of the procedure compared with the risk of waiting. This method needs to be further defined with objective measurements and tested in clinical trials to determine whether it is associated with improved outcomes and reduced resource use.

In conclusion, the decision to initiate KST is most often individualized according to the patient’s comorbidities, severity of illness, trajectory of kidney function and urine output, as well as requirements for fluid balance and solute removal. Clinical judgment concerning the need for, or avoidance of, KST initiation may be complemented with additional tools to stratify the risk, such as the demand-capacity mismatch concept, kidney damage and functional biomarkers, and the FST to provide more timely interventions and improve outcomes. A delayed approach could translate into a potentially reduced burden of dialysis dependence or lower health resources utilization. However, we must ascertain what constitutes the waiting period and the benefits and risks associated with this approach. Additional research in this area needs to be coupled with understanding practice variations to inform personalized patient management.

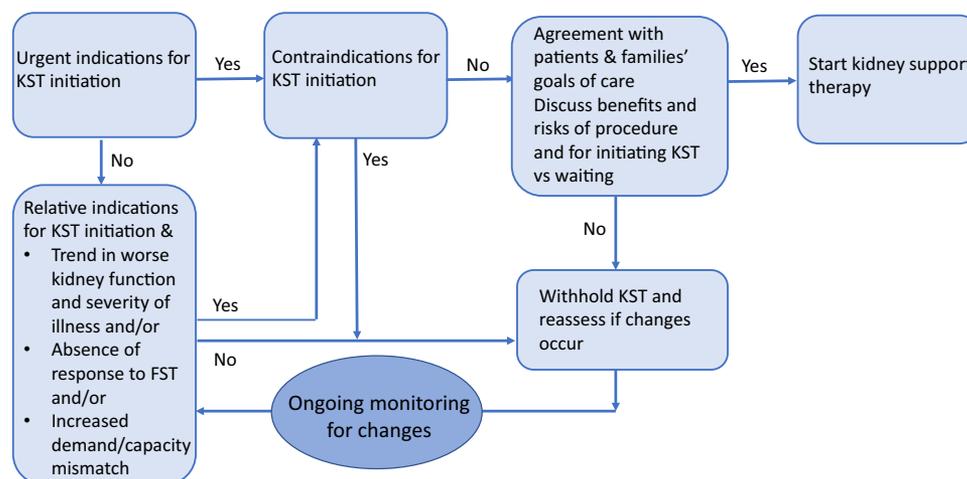


Figure 1. Approach to assessment of KST initiation. Urgent indications for KST include severe hyperkalemia (>6.5 mmol/L), acidosis (pH < 7.2), or pulmonary edema refractory to medical treatment; and uremic pericarditis or encephalopathy. Relative contraindications to KST include futility considering the global prognosis (palliative care, limited survival regardless of KST), and high likelihood of dialysis dependence if long-term dialysis is unacceptable. Abbreviations: FST, furosemide stress test; KST, kidney support therapy.

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