Renal Replacement Therapy Controversies

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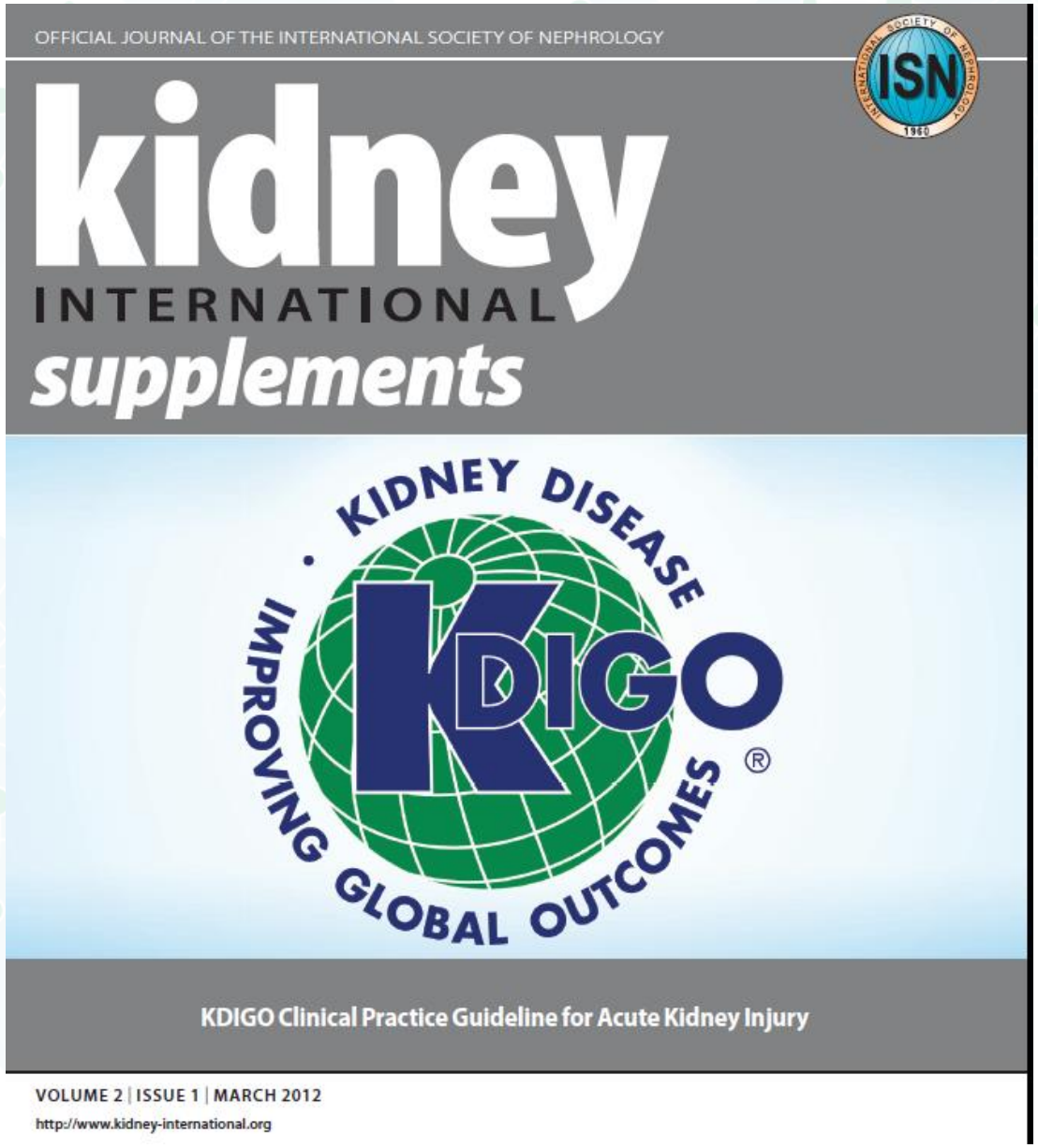
The impact of KDIGO (March 2012)



KDIGO on RRT

Section 5: Dialysis Interventions for Treatment of AKI

5.1.1: Initiate RRT emergently when life-threatening changes in fluid, electrolyte, and acid-base balance exist. (*Not Graded*)

5.1.2: 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*)

5.2.1: 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*)

5.2.2: We suggest not using diuretics to enhance kidney function recovery, or to reduce the duration or frequency of RRT. (*2B*)

5.3.1: In a patient with AKI requiring RRT, base the decision to use anticoagulation for RRT on assessment of the patient's potential risks and benefits from anticoagulation (see Figure 17). (*Not Graded*)

- 5.3.1.1: We recommend using anticoagulation during RRT in AKI if a patient does not have an increased bleeding risk or impaired coagulation and is not already receiving systemic anticoagulation. (*1B*)

5.3.2: For patients without an increased bleeding risk or impaired coagulation and not already receiving effective systemic anticoagulation, we suggest the following:

- 5.3.2.1: For anticoagulation in intermittent RRT, we recommend using either unfractionated or low-molecular-weight heparin, rather than other anticoagulants. (*1C*)
- 5.3.2.2: For anticoagulation in CRRT, we suggest using regional citrate anticoagulation rather than heparin in patients who do not have contraindications for citrate. (*2B*)
- 5.3.2.3: For anticoagulation during CRRT in patients who have contraindications for citrate, we suggest using either unfractionated or low-molecular-weight heparin, rather than other anticoagulants. (*2C*)

KDIGO on RRT

5.3.3: For patients with increased bleeding risk who are not receiving anticoagulation, we suggest the following for anticoagulation during RRT:

5.3.3.1: We suggest using regional citrate anticoagulation, rather than no anticoagulation, during CRRT in a patient without contraindications for citrate. *(2C)*

5.3.3.2: We suggest avoiding regional heparinization during CRRT in a patient with increased risk of bleeding. *(2C)*

5.3.4: In a patient with heparin-induced thrombocytopenia (HIT), all heparin must be stopped and we recommend using direct thrombin inhibitors (such as argatroban) or Factor Xa inhibitors (such as danaparoid or fondaparinux) rather than other or no anticoagulation during RRT. *(1A)*

5.3.4.1: In a patient with HIT who does not have severe liver failure, we suggest using argatroban rather than other thrombin or Factor Xa inhibitors during RRT. *(2C)*

5.4.1: We suggest initiating RRT in patients with AKI via an uncuffed nontunneled dialysis catheter, rather than a tunneled catheter. *(2D)*

5.4.2: When choosing a vein for insertion of a dialysis catheter in patients with AKI, consider these preferences *(Not Graded)*:

- First choice: right jugular vein;
- Second choice: femoral vein;
- Third choice: left jugular vein;
- Last choice: subclavian vein with preference for the dominant side.

5.4.3: We recommend using ultrasound guidance for dialysis catheter insertion. *(1A)*

5.4.4: We recommend obtaining a chest radiograph promptly after placement and before first use of an internal jugular or subclavian dialysis catheter. *(1B)*

5.4.5: We suggest not using topical antibiotics over the skin insertion site of a nontunneled dialysis catheter in ICU patients with AKI requiring RRT. *(2C)*

5.4.6: We suggest not using antibiotic locks for prevention of catheter-related infections of nontunneled dialysis catheters in AKI requiring RRT. *(2C)*

KDIGO on RRT

5.5.1: We suggest to use dialyzers with a biocompatible membrane for IHD and CRRT in patients with AKI. (*2C*)

5.6.1: Use continuous and intermittent RRT as complementary therapies in AKI patients. (*Not Graded*)

5.6.2: We suggest using CRRT, rather than standard intermittent RRT, for hemodynamically unstable patients. (*2B*)

5.6.3: We suggest using CRRT, rather than intermittent RRT, for AKI patients with acute brain injury or other causes of increased intracranial pressure or generalized brain edema. (*2B*)

5.7.1: We suggest using bicarbonate, rather than lactate, as a buffer in dialysate and replacement fluid for RRT in patients with AKI. (*2C*)

5.7.2: We recommend using bicarbonate, rather than lactate, as a buffer in dialysate and replacement fluid for RRT in patients with AKI and circulatory shock. (*1B*)

5.7.3: We suggest using bicarbonate, rather than lactate, as a buffer in dialysate and replacement fluid for RRT in patients with AKI and liver failure and/or lactic acidemia. (*2B*)

5.7.4: We recommend that dialysis fluids and replacement fluids in patients with AKI, at a minimum, comply with American Association of Medical Instrumentation (AAMI) standards regarding contamination with bacteria and endotoxins. (*1B*)

5.8.1: The dose of RRT to be delivered should be prescribed before starting each session of RRT. (*Not Graded*) We recommend frequent assessment of the actual delivered dose in order to adjust the prescription. (*1B*)

5.8.2: Provide RRT to achieve the goals of electrolyte, acid-base, solute, and fluid balance that will meet the patient's needs. (*Not Graded*)

5.8.3: We recommend delivering a Kt/V of 3.9 per week when using intermittent or extended RRT in AKI. (*1A*)

5.8.4: We recommend delivering an effluent volume of 20–25 ml/kg/h for CRRT in AKI *(1A)*. This will usually require a higher prescription of effluent volume. (*Not Graded*)

KDIGO and RRT 8 years later

- Knowledge has expanded
- Trials have been completed
- Large observational studies have been published
- Technology has evolved
- Pathophysiological understanding has increased
- New drugs have been developed
- Social perspectives have changes
- **Controversies however remain and have evolved with further knowledge**
- **KDIGO remains committed to improving the care of patients with AKI**
- **KDIGO meeting in Rome in April 2019 on AKI controversies**

CONTROVERSY 1: IS THE TERMINOLOGY "RRT" SUFFICIENTLY ACCURATE, DESCRIPTIVE AND PATIENT-CENTERED)?

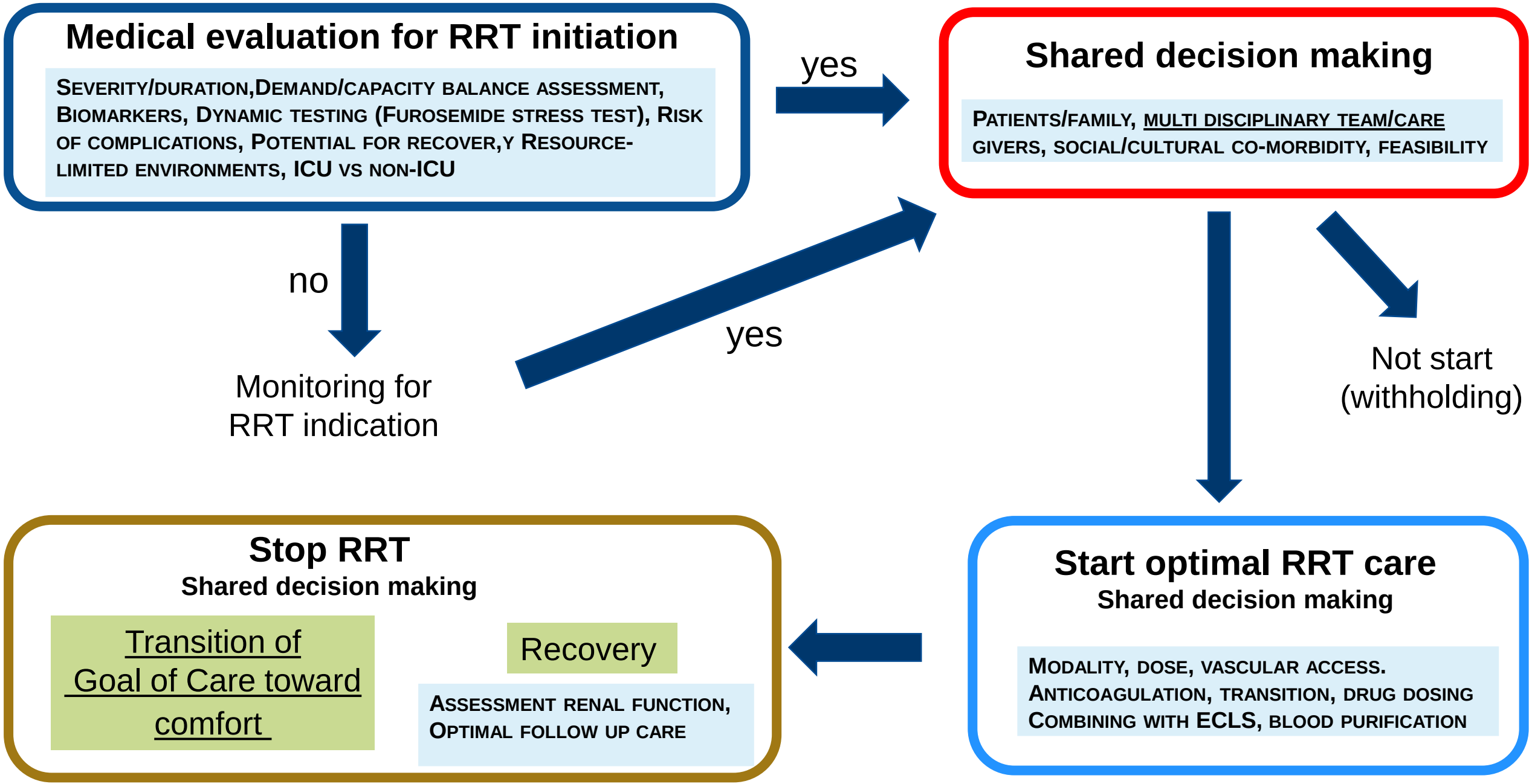
- Since KDIGO 2012, there has been concern the term "renal" has been placed by "kidney" and whether the term "replacement" is appropriate rather than "support" or "partial replacement".
- **No prior KDIGO statement**
- The implications of changes in nomenclature are not insignificant.
- Knowledge gaps/future directions to be addressed.

Principles of communication, terminology and care

- On behalf of all AKI Patients and their families and/or medical decision makers, we recommend that patients be the focus of all communication and care. Thus, whenever possible all decisions about treatment should be shared with patients, their families and/or next of kin and, if required all of the end-of-life-care multidisciplinary team.
- All communication with patients and their supporting families/friends, should be in simple lay language, at regular intervals with the awareness that these people are traumatised (for example: Life Support, Kidney Machine, or similar words are preferred to term likes RRT).
- If RRT becomes permanent and the patient enters chronic dialysis pathway, we recommend that all relevant medical or nursing personnel should change their language to the type used for chronic RRT (like transplant, hemodialysis and peritoneal dialysis).

Controversy	Response to controversy
Terminology “RRT”	1. We strongly recommend that **”medical terms” be avoided**, and “lay terms” be used when communicating with patients. 2. We recommend that **Health Care Professional** should communicate to the family using “Lay terms” 3. We recommend that current medical language for communication among health care professional remain unchanged

Schematic diagram of RRT decision in AKI



CONTROVERSY 2: WHAT CRITERIA SHOULD BE USED TO INITIATE RRT IN PATIENTS WITH AKI?

- Since KDIGO 2012, considerable additional evidence have been published. As such, we believe these statements should be re-evaluated and updated, if appropriate.
- **KDIGO statements (5.1.1-5.1.2)**
- There have been several RCTs and observational data published on this theme that necessitates analysis and interpretation.
- Knowledge gaps/future directions to be addressed.

Trials of “early” vs. “delayed” RTT

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit

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BACKGROUND

The timing of renal-replacement therapy in critically ill patients who have acute kidney injury but no potentially life-threatening complication directly related to renal failure is a subject of debate.

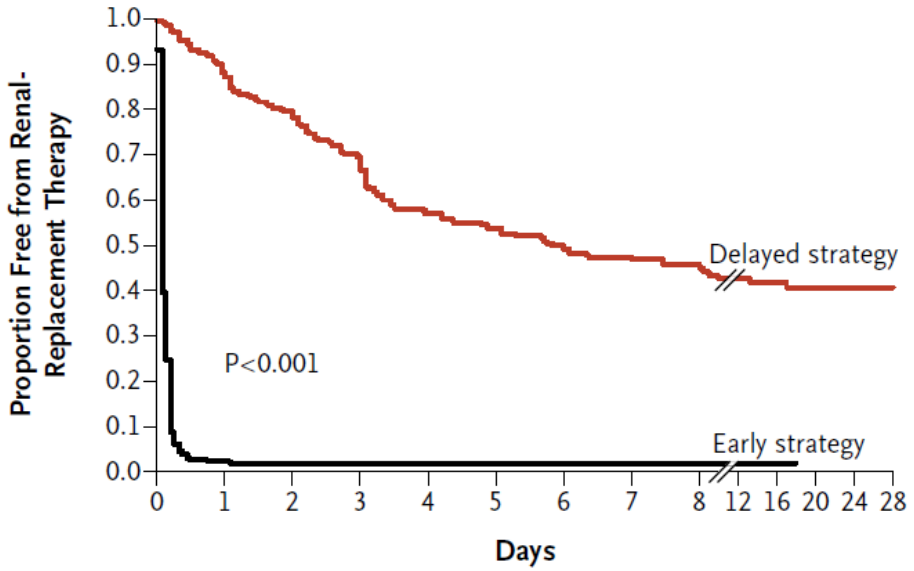
All patients had to have stage 3 KDIGO to be randomized
So – no one received "early" RRT

METHODS

In this multicenter randomized trial, we assigned patients with severe acute kidney injury (Kidney Disease: Improving Global Outcomes [KDIGO] classification, stage 3 [stages range from 1 to 3, with higher stages indicating more severe kidney injury]) who required mechanical ventilation, catecholamine infusion, or both and did not have a potentially life-threatening complication directly related to renal failure to either an early or a delayed strategy of renal-replacement therapy. With the early strategy, renal-replacement therapy was started immediately after randomization. With the delayed strategy, renal-replacement therapy was initiated if at least one of the following criteria was met: severe hyperkalemia, metabolic acidosis, pulmonary edema, blood urea nitrogen level higher than 112 mg per deciliter, or oliguria for more than 72 hours after randomization. The primary outcome was overall survival at day 60.

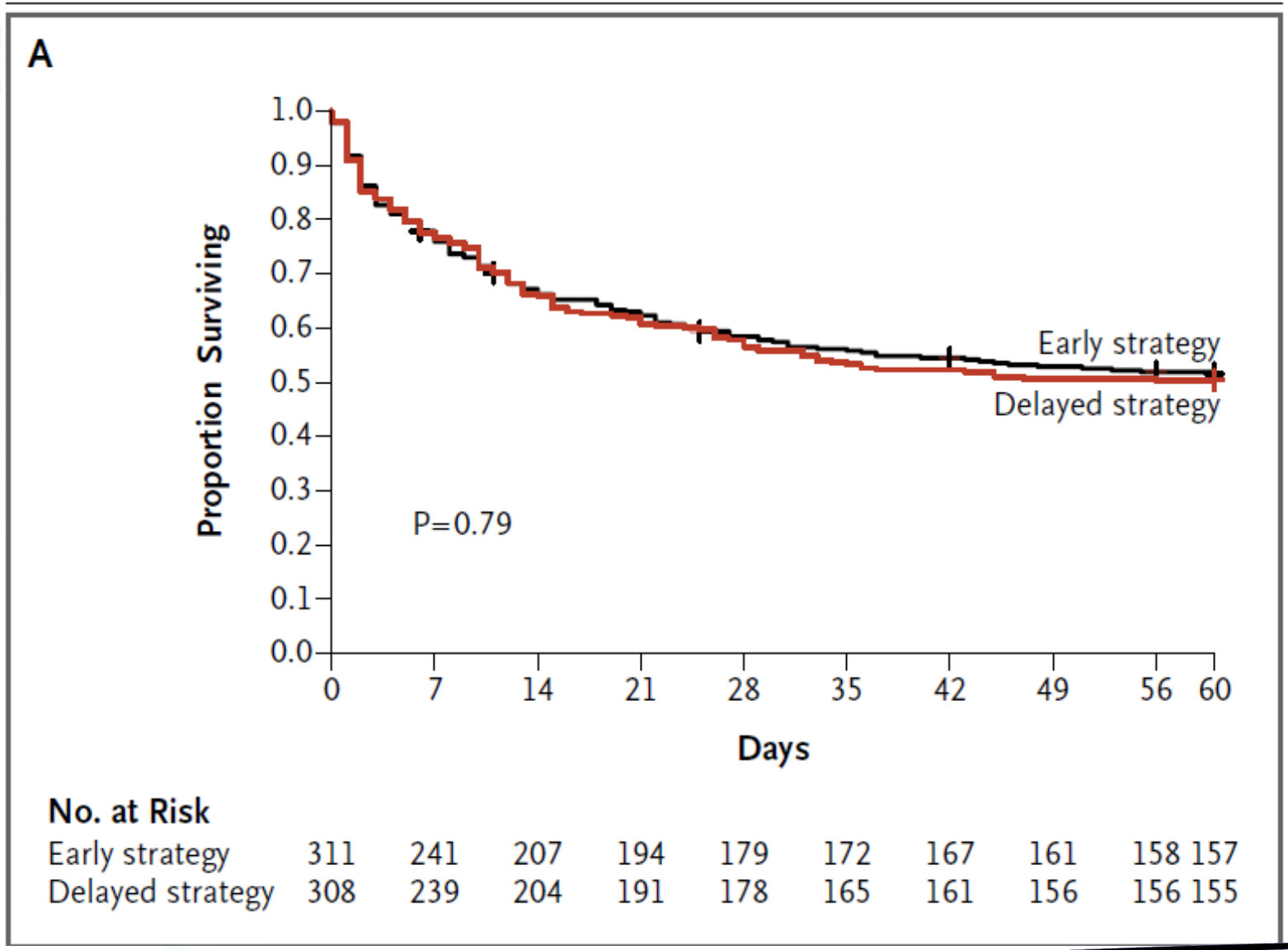
Physiological support — no. (%)		
Invasive mechanical ventilation	266 (86)	267 (87)
Vasopressor support with epinephrine or norepinephrine	265 (85)	263 (85)

B



Median norepinephrine dose = 70 mcg/min

First modality– no. (%)			0.97
Intermittent RRT	169 (56)	86 (55)	
Continuous RRT	135 (44)	71 (45)	
RRT modalities during ICU stay– no. (%)			0.62
Intermitent RRT only	142 (47)	73 (47)	
Continuous RRT only	101 (33)	47 (30)	
Both modalities (intermittent and continuous)	61 (20)	37 (24)	


A
Proportion Surviving
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Early strategy
Delayed strategy
P=0.79
0
7
14
21
28
35
42
49
56
60
Days
No. at Risk
Early strategy 311 241 207 194 179 172 167 161 158 157
Delayed strategy 308 239 204 191 178 165 161 156 156 155

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

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

Alexander Zarbock, MD; John A. Kellum, MD; Christoph Schmidt, MD; Hugo Van Aken, MD; Carola Wempe, PhD; Hermann Pavenstädt, MD; Andreea Boanta, MD; Joachim Gerß, PhD; Melanie Meersch, MD

IMPORTANCE Optimal timing of initiation of renal replacement therapy (RRT) for severe acute kidney injury (AKI) but without life-threatening indications is still unknown.

OBJECTIVE To determine whether early initiation of RRT in patients who are critically ill with AKI reduces 90-day all-cause mortality.

DESIGN, SETTING, AND PARTICIPANTS Single-center randomized clinical trial of 231 critically ill patients with AKI Kidney Disease: Improving Global Outcomes (KDIGO) stage 2 (≥2 times baseline or urinary output <0.5 mL/kg/h for ≥12 hours) and plasma neutrophil gelatinase–associated lipocalin level higher than 150 ng/mL enrolled between August 2013 and June 2015 from a university hospital in Germany.

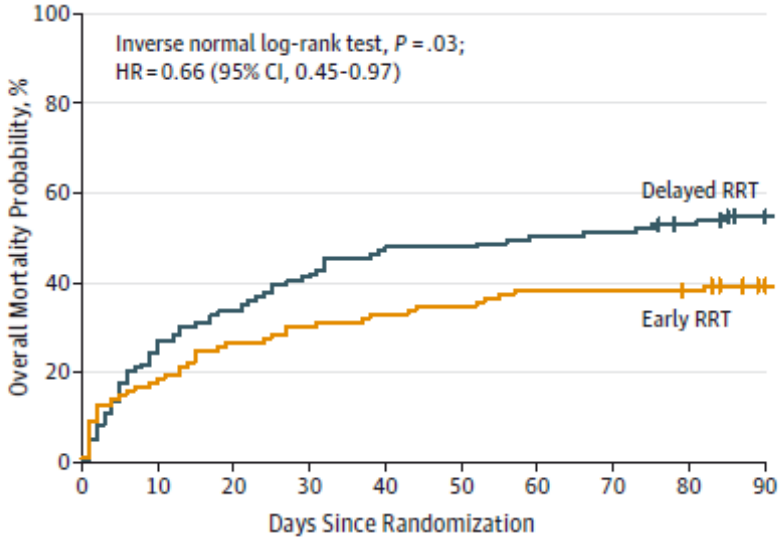
INTERVENTIONS Early (within 8 hours of diagnosis of KDIGO stage 2; n = 112) or delayed (within 12 hours of stage 3 AKI or no initiation; n = 119) initiation of RRT.

Table 1. Baseline Characteristics for Critically Ill Patients Receiving Early vs Delayed Initiation of Renal Replacement Therapy

	Early (n = 112)	Delayed (n = 119)
Age, mean (SD), y	65.7 (13.5)	68.2 (12.7)
Sex, No. (%)		
Men	78 (69.6)	68 (57.1)
Women	34 (30.4)	51 (42.9)
Baseline creatinine, mean (SD), mg/dL	1.1 (0.4)	1.1 (0.4)
Estimated GFR, mean (SD), mL/min/1.73 m^2	56.2 (13.8)	55.9 (14.5)
SOFA score, mean (SD)	15.6 (2.3)	16.0 (2.3)
APACHE II, mean (SD)	30.6. (7.5)	32.7 (8.8)
Comorbidities, No. (%)		
Hypertension	97 (86.6)	92 (77.3)
Congestive heart failure	49 (43.8)	47 (39.5)
Diabetes	17 (15.2)	28 (23.5)
Chronic obstructive pulmonary disease	20 (17.9)	21 (17.6)
Chronic kidney disease (estimated GFR<60)	42 (37.8)	52 (44.8)
Cardiac arrhythmia	37 (33.0)	53 (44.5)
Source of admission, No./total No. (%)		
Cardiac		
Total	56/112 (50.0)	52/119 (43.7)
CABG only	11/56 (19.6)	16/52 (30.8)
Valve only	13/56 (23.2)	10/52 (19.2)
Combination or others	32/56 (57.1)	26/52 (50.0)
Trauma	14/112 (12.5)	14/119 (11.8)
Abdominal		
Total	34/112 (30.4)	44/119 (37.0)
Bowel resection	8/34 (23.5)	5/44 (11.4)
Esophageal resection	5/34 (14.7)	2/44 (4.5)
Liver transplant	3/34 (8.8)	7/44 (15.9)
Others	18/34 (52.9)	30/44 (68.2)
Others	8/112 (7.1)	9/119 (7.6)
Neurosurgical	2/8 (25.0)	3/9 (33.3)
Pulmonary	6/8 (75.0)	6/9 (66.7)
Medication, No. (%)		
Vasopressors	96 (85.7)	108 (90.8)

First treatment: CRRT in all patients

Figure 2. Mortality Probability Within 90 Days After Study Enrollment for Patients Receiving Early and Delayed Initiation of Renal Replacement Therapy (RRT)



No. at risk

Early RRT	112	92	82	78	75	73	69	69	66	55
Delayed RRT	119	90	79	70	63	62	59	58	54	48

KDIGO indicates Kidney Disease: Improving Global Outcomes. In the delayed group, 18 patients had an absolute indication for RRT. The median (quartile 1 [Q1], quartile 3 [Q3]) duration of follow-up was 90 days (Q1, Q3: 90, 90) in the early group and 90 days (Q1, Q3: 90, 90) in the delayed group. The vertical ticks indicate censored cases.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Timing of Renal-Replacement Therapy in Patients with Acute Kidney Injury and Sepsis

S.D. Barbar, R. Clere-Jehl, A. Bourredjem, R. Hernu, F. Montini, R. Bruyère, C. Lebert, J. Bohé, J. Badie, J.-P. Eraldi, J.-P. Rigaud, B. Levy, S. Siami, G. Louis, L. Bouadma, J.-M. Constantin, E. Mercier, K. Klouche, D. du Cheyron, G. Piton, D. Annane, S. Jaber, T. van der Linden, G. Blasco, J.-P. Mira, C. Schwebel, L. Chimot, P. Guiot, M.-A. Nay, F. Meziani, J. Helms, C. Roger, B. Louart, R. Trusson, A. Dargent, C. Binquet, and J.-P. Quenot, for the IDEAL-ICU Trial Investigators and the CRICS TRIGGERSEP Network*

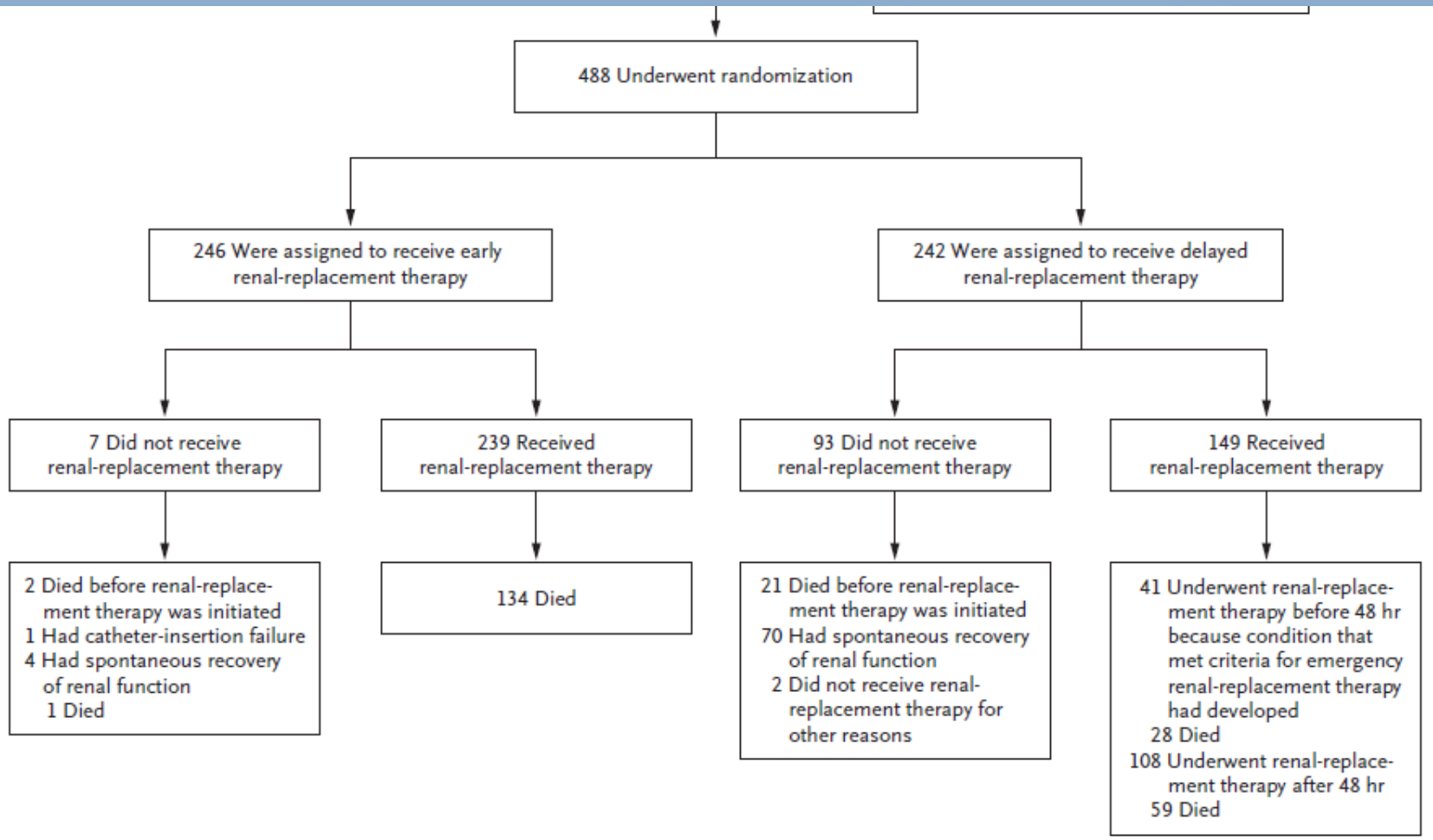
BACKGROUND

Acute kidney injury is the most frequent complication in patients with septic shock and is an independent risk factor for death. Although renal-replacement therapy is the standard of care for severe acute kidney injury, the ideal time for initiation remains controversial.

Not early vs. late – Late vs. later

METHODS

In a multicenter, randomized, controlled trial, we assigned patients with early-stage septic shock who had severe acute kidney injury at the failure stage of the risk, injury, failure, loss, and end-stage kidney disease (RIFLE) classification system but without life-threatening complications related to acute kidney injury to receive renal-replacement therapy either within 12 hours after documentation of failure-stage acute kidney injury (early strategy) or after a delay of 48 hours if renal recovery had not occurred (delayed strategy). The failure stage of the RIFLE classification system is characterized by a serum creatinine level 3 times the baseline level (or ≥4 mg per deciliter with a rapid increase of ≥0.5 mg per deciliter), urine output less than 0.3 ml per kilogram of body weight per hour for 24 hours or longer, or anuria for at least 12 hours. The primary outcome was death at 90 days.



Multiple organ support in ICU — no. (%)		
Invasive mechanical ventilation	219 (89)	213 (88)
Vasopressor support with norepinephrine or epinephrine	246 (100)	242 (100)
Inotropic support with dobutamine	52 (21)	58 (24)
Extracorporeal membrane oxygenation	1 (<1)	9 (4)

Patients who received RRT — no. (%)	239 (97%)	149 (62%)	<0.001
CRRT only	111 (46%)	68 (46%)	0.88
IHD only	82 (34%)	50 (34%)	0.88
CRRT and IHD	46 (19%)	31 (21%)	0.71

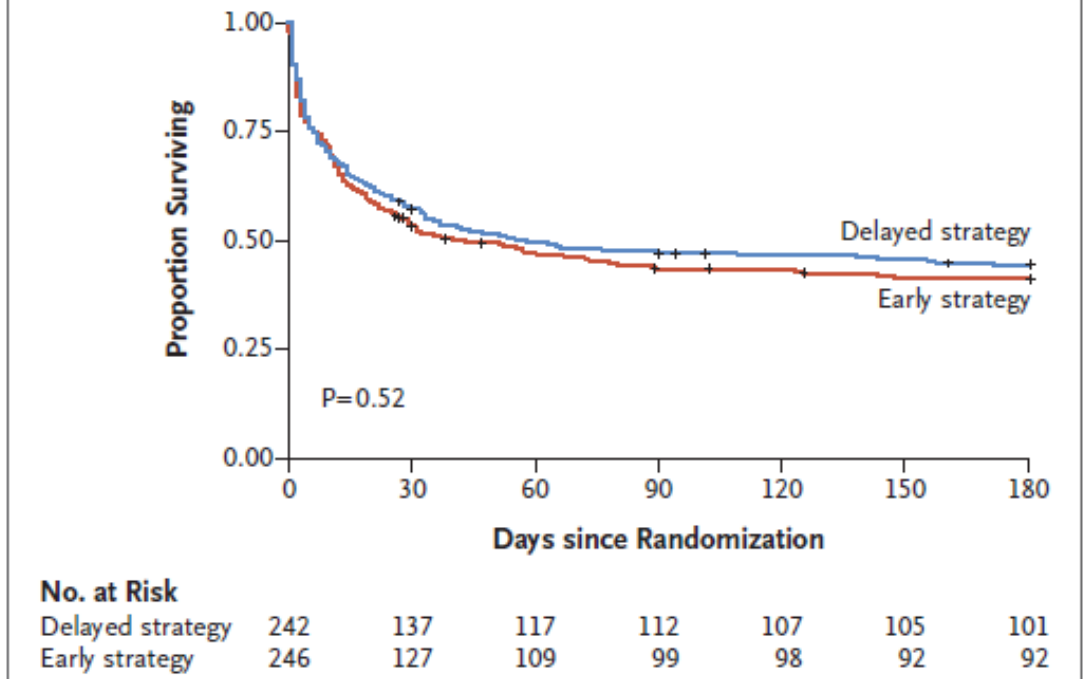


Figure 2. Overall Survival among Patients Assigned to Early Renal-Replacement Therapy and Delayed Renal-Replacement Therapy.

In the early-strategy group, renal-replacement therapy was initiated within 12 hours after documentation of acute kidney injury. In the delayed-strategy group, renal-replacement therapy was initiated 48 hours after the documentation of acute kidney injury, if renal recovery had not occurred. If criteria for emergency renal-replacement therapy were met by a patient in this group, renal-replacement therapy was initiated as soon as possible. The tick marks indicate censored data. The P value is for the comparison of overall survival between the two groups.

Statistical Analysis Plan for the Standard versus Accelerated Initiation of Renal Replacement Therapy in Acute Kidney Injury (STARRT-AKI) trial

Trial Design

The STARRT-AKI is a multi-national randomized open-label controlled trial of critically ill patients with severe AKI that will compare the clinical effectiveness and cost-effectiveness of a pre-emptive (accelerated) strategy versus a strategy of watchful waiting and RRT initiation guided by AKI-related indications and clinician judgment (standard).[9] The protocol was finalized on October 5, 2015, without intervening amendments.[10]

3,000 patients in 170 centers and 15 countries

Recruitment to be completed this year

Inclusion criteria are (all must be fulfilled):

1. Age ≥18 years on the day of eligibility screening;
2. Admission to a critical care unit;
3. Evidence of kidney dysfunction (serum creatinine [sCr] ≥100 µmol/L [women] and ≥130 µmol/L [men] based on last bloodwork available prior to screening); and
4. Evidence of severe AKI based on at least ONE of the following three criteria: i) 2-fold increase in sCr from baseline; OR ii) current sCr is >354 µmol/L with a minimum increase of 27 µmol/L from the baseline sCr; OR iii) urine output <6 mL/kg in the prior 12 hours.

Exclusion criteria are (none may be present):

- Potassium at time of screening ≥5.5 mmol/L;
- Bicarbonate at time of screening ≤15 mmol/L;
- Presence of a drug overdose or dialyzable toxin that necessitates RRT;
- Lack of commitment to provide RRT as part of philosophy of care;
- Receipt of any RRT in past 2 months;
- Kidney transplant within the past 365 days;
- Known advanced chronic kidney disease (CKD), defined by an eGFR <20 mL/min/1.73 m^2;
- Presence or clinical suspicion of renal obstruction, rapidly progressive glomerulonephritis, vasculitis, thrombotic microangiopathy or acute interstitial nephritis

1. Clinician(s) caring for patient believe(s) that immediate RRT is mandated. This will be defined by, after fulfilling the above inclusion/exclusion criteria, the study team will speak to the ICU and/or nephrology attending physician and ask if he/she agrees with statement: “RRT must be initiated immediately in this patient.”
If the answer is “Yes”, the patient will be excluded;

2. Clinician(s) caring for patient believe(s) that deferral of RRT is mandated. This will be defined by, after fulfilling the above inclusion/exclusion criteria, the study team will speak to the ICU and/or nephrology attending physician and ask if he/she agrees with statement: “RRT must be deferred in this patient.”
If the answer is “Yes”, the patient will be excluded, but may be re-screened for eligibility.

Controversy	Response to controversy
Demand/capacity balance	We suggest that acute RRT should be considered when **metabolic and fluid demands exceed the kidney' capacity to meet them.** As demand–capacity imbalance is dynamic, we suggest that it should be evaluated regularly .
Severity/duration	We suggest that KDIGO staging thresholds, particularly in isolation, **not YET be used** as indications for RRT initiation in AKI.
Biomarkers	We recommend that kidney biomarkers **not be used in isolation for decision-making** for RRT initiation.
Dynamic test (Furosemide stress test)	We suggest that use of **a standardized FST can be used in stage AKI 1-2 to further quantify likelihood of AKI progression and be integrated into the spectrum of clinical information** available when planning and deciding to initiate RRT.
Risk for complications	We recommend a **shared decision-making process** be considered for all critically ill patients with AKI**.** This should integrates the risk of complications, global prognosis and patient preferences, and be undertaken when considering starting or not starting RRT
Potential for recovery	We recommend that **a shared decision-making process**, be considered when offering and starting RRT for patients with AKI. This should include integrating the probability of recovery to RRT independence, global prognosis (i.e., baseline burden of disease, acuity, course) and patient preferences for both acute treatment and kidney recovery,
Resource-limited environments	We acknowledge the challenges and resources constraint of both HIC and LMIC settings. However we recommend **a similar approach** be undertaken for considering who and when to start RRT
ICU vs outside the ICU	We recommend **a similar approach** be undertaken for considering who and when to start RRT in both ICU and non-ICU settings

CONTROVERSY 3: WHAT IS THE OPTIMAL STRATEGY (INCLUDING MODALITY) FOR PROVIDING ACUTE RRT?

- Since KDIGO 2012, there have been some advances that need to be addressed.
- **KDIGO statements (5.2.1-5.8.4)**
- Several studies have generated new evidence on the catheter/access, modality, filter types, technological machine advances, dose, anticoagulation, medication prescription etc.
- There have been several trials and observational data published on this theme that necessitates analysis and interpretation.
- Knowledge gaps/future directions to be addressed.

Controversy	Response to controversy
MODALITY	1) Patients with AKI requiring RRT have an evolving clinical status and should be supported by the appropriate and available modality. **2) In hemodynamically compromised patients, CRRT, rather than IHD, is more physiologically appropriate.** **3) Modalities choice (CRRT, IHD, PD, SLED/PIRRT) for initial and transition should be tailored to patients clinical status**. 4) CRRT, rather that intermittent RRT, should be used in patients with **raised intracerebral pressure and AKI.** 5) Selection of modalities should be considered in the context of **available resources and expertise of personnel.**
Vascular access	1) An **uncuffed non-tunneled dialysis catheter of appropriate length and gauge** should be used to initiate RRT in AKI patients. In patients with expected prolonged indication for RRT due to the underlying clinical state such as CKD and expected survival, a cuffed catheter can be considered. 2) First choice: right jugular vein, Second choice: femoral vein, Third choice: left jugular vein, Last choice: subclavian vein
Anticoagulation	1) Anticoagulation type should be selected **based on local resources and expertise of personnel.** 2) Regional citrate anticoagulation for CRRT should be used in patients who do not have contraindications to it.

Controversy	Response to controversy
Dosage	1) Delivery of RRT must reach **the goals of electrolyte, acid-base, solute, and fluid balance** that will meet the patient's needs. 2) A Kt/V of 1.2 per treatment three times a week should at least be delivered when using intermittent or extended RRT. 3) For PD further studies need to focus on dosing in AKI. Until then, we suggest a dose of 0.3 Kt/V per session 4) An effluent volume of 20-25 ml/kg/h should be delivered when CRRT should at least be used. This will usually **require a higher prescription of effluent volume.**
Transition/ Discontinuation	1) RRT should be discontinued when it is **no longer required**, either because kidney function has recovered, or because RRT is **no longer consistent with the shared goals of care**. 2) **Modality transition** from CRRT to IHD in ICU patients should be considered when **vasopressor support has been stopped, when intracranial hypertension is not a concern, and when positive fluid balance cannot be controlled by IHD.**
Drug adjustment	1) **Evaluate primary literature** for drug dosing studies 2) When available, **therapeutic drug monitoring (TDM) should be used**, especially for drugs with narrow therapeutic index. 3) Clearance (CL) of some drugs correlates very closely with CLcr. 4) Consider mechanism of action of the drug and pharmacodynamic evaluation of therapy ie. AUC/MIC ratios for the pathogen targeted.

CONTROVERSY 4: HOW SHOULD RRT BE APPLIED IN THE CONTEXT OF MULTI-ORGAN SUPPORT (A. ECLS; B. BLOOD PURIFICATION)?

- Since KDIGO 2012, there have been significant advances and greater utilization in ECLS (i.e., ECMO, $ECCO_2R$) and greater evidence published on blood purification therapies in critically ill patients.
- **No prior KDIGO statement**
- Several questions on the optimal approach to patient selection, techniques, timing/indications; circuit integration; monitoring for ECLS and concomitant blood purification techniques remain uncertain and unresolved.
- There have been a number of trials observational data published on this theme that necessitates analysis and interpretation.
- Knowledge gaps/future directions to be addressed.

Controversy	Response to controversy
Optimal technique (monitoring) in combining RRT with ECCO2R/ECMO **- Using Side-Arm of ECCO2R/ECMO circuite instead of using separate circuit**	1. We recommend the decision of how to combine RRT with **ECCO2R/ECMO should depend on the local expertise, technology, and human resources** available. 2. We recommend that such combine treatment should be based on **multidisciplinary approach.** **3. We recommend that more studies be performed to define** the best strategy for training and practice.
All RRT techniques should be performed by a continuous modality during RRT combining with ECCO2R/ECMO	1. Although different RRT modalities can be used to support these patients during ECCO2R/ECMO, and **comparative studies are not available.** Because of hemodynamic status, we suggest that CRRT is more appropriate **in this setting.** 2. We recommend a **Registry incorporating current definitions of AKI** focused on patient receiving ECLS-RRT to understand epidemiology, technology, indications and complications associated with current practice.

Controversy	Response to controversy
Indication for combining RRT with ECCO2R and ECMO	1. There is **no clear evidence** supporting that usual RRT indications should vary according to the presence or the absence of an ECMO/ECCO2R circuit. 2. Nonetheless, patients for whom ECMO or ECCO2R is required are known to be very sensitive to fluid overload. Therefore, in patients with ECMO/ECCO2R, earlier RRT (as compared to patients without ECMO/ECCO2R) may be required as part of the appropriate management of fluid overload. 3. We recommend **a registry** enrolling patients combining ECMO/ECCO2R AND RRT to better understand the current precise indications for initiating RRT in patients (adults and children) with ECMO/ECCO2R and fluid managment in this setting.
Optimal blood flow in ECCO2R	1. **There is no consensus on the blood flow rate** that should be applied with ECCO2R in clinical practice. It is therefore unclear whether ECCO2R could be efficiently applied in a system combining RRT and ECCO2R. 2. We recommend research focused on this technical aspect.
Optimal Dialysate/ Replacement fluid composition during combining RRT with ECCO2R and ECMO	1. Respiratory dialysis (ECCO2R and ECMO) with modified dialysis solutions is currently limited to in vitro and experimental studies 2. We recommend research focused on this technical aspect.

Controversy	Response to controversy
Anticoagulation in RRT circuit during combining RRT with ECCO2R and ECMO	1. Anticoagulation of RRT circuit when ECMO/ECCO2R is already running is **not standardized** 2. The administration of heparin may **depend on patient factors** (e.g. risk of bleeding), circuit set-up (e.g. connection to patient or to ECMO) and **institutional protocols.** 3. There is currently no recommendation to provide: it is **possible to have RRT circuits without dedicated heparin in this setting** unless excessively frequent clotting is observed 4. We recommne that study be conducted to compare different anticoagulation strategies in this setting.
Citrate anticoagulation in RRT circuit during combining RRT with ECCO2R and ECMO	1. Citrate anticoagulation during RRT added to ECMO/ECCO2R is **possible**. 2. Its feasibility and performance compared to other forms of anticoagulation remain untested 3. We recommend comparative studies of citrate anticoagulation in this setting.

CONTROVERSY 5: HOW DO RRT DECISIONS AFFECT LONG TERM OUTCOMES AND HOW SHOULD PATIENTS BE FOLLOWED?

- Since KDIGO 2012, there have been greater recognition of the importance of and new evidence published on long-term outcomes among patients treated with RRT.
- **No prior KDIGO statement**
- There have been trials and observational data published on this theme that necessitates analysis and interpretation.
- Knowledge gaps/future directions to be addressed.

Controversy	Response to controversy
Choice of RRT modality and impact on renal recovery	The selection of **RRT modality does not appear to have a major impact** on recovery of renal function. Selection of modality of RRT should therefore be based on shared decision making, local expertise, logistic factors, and patient characteristics. **eGFR in conjunction with MAKE** has been used for medium and long term assessment but has several limitations. There is **uncertainty about the best way to measure renal recovery after RRT** in both the short and medium term. However, proteinuria is associated with worse long term outcomes and it is easy to measure.
Assessment of renal function for renal recovery	1. We recommend **patient-centered outcomes (quality of life, functional recovery)** along with patient experience after recovery are priority and need to be assessed. 2. We recommend that **post AKI proteinuria** should be measured given its association with adverse outcomes.

Controversy	Response to controversy
Optimal Follow-up for AKI patients	1. **Shared decision making** and communication between caregivers, patient and family members is crucial to patient recovery 2. **Patients recovering from critical illness** and AKI are often discharged to rehabilitation/skilled nursing facilities **need close monitoring** to ensure adequate overall recovery to baseline state of health and well-being. 3. We recommend that such patients receive multidisciplinary recovery focused care. 4. Patients with AKI who continue to require RRT at hospital discharge often receive HD in outpatient ESKD dialysis facilities. Patients with congestive heart failure are less likely to recover renal function. Higher UF rates and more intradialytic hypotensive episodes are associated with higher non-recovery of renal function. We recommend **careful monitoring of hemodynamic** status **intravascular volume, and urine outp**ut during dialysis to assess for renal recovery.

CONTROVERSY 6: WHAT MINIMUM SPECTRUM OF QUALITY INDICATORS SHOULD BE IMPLEMENTED AND MONITORING FOR PATIENTS RECEIVING ACUTE RRT?

- Since KDIGO 2012, there have been growing data on the important of measuring and monitoring the quality of acute RRT provided to critically ill patients with AKI, including the optimal "benchmarking" for acute RRT programs.
- **No prior KDIGO statement**
- There have been evidence published and a dedicated ADQI focused on this theme that necessitates analysis and interpretation.
- Knowledge gaps/future directions to be addressed.

Controversy	Response to controversy
Quality indicators	1. We recommend that **quality of acute RRT should be monitored** to ensure the effective and safe delivery of care. 2. We recommend that at a minimum this should **include the integration, monitoring and reporting of structure, process and outcome indicators** across all forms of acute RRT therapies. 3. We recommend that outcome measures should comprise a variety of metrics that **incorporate patient survival, patient-centered acute RRT outcomes, safety, AKI survivor-related outcomes, and patient experience.**

Conclusions

- The field of RRT has seen major changes since the KDIGO 2012 statement
- New controversies have emerged
- Old ones have evolved
- Social values have changed
- Trials have provided new evidence
- The biggest RRT trial is about to be completed
- Nephrologists and Intensivists need to be aware of such new concepts, ideas and controversies to practice at the highest level of excellence