Strategies for Starting Renal Replacement Therapy in Acute Kidney Injury

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- **Data Safety Monitoring Committee:** La Jolla Pharmaceutical
- **Co-PI:** STARRT-AKI trial (NCT02568722)

Objectives

1. Review recent clinical practice guideline statements for when to start RRT in AKI
2. Review accumulated evidence evaluating timing of RRT in critically ill patients AKI
3. Review recent randomized trials on optimal timing of RRT in AKI (AKIKI, ELAIN and STARRT-AKI)

Changing Incidence and Outcomes Following Dialysis-Requiring Acute Kidney Injury Among Critically Ill Adults: A Population-Based Cohort Study

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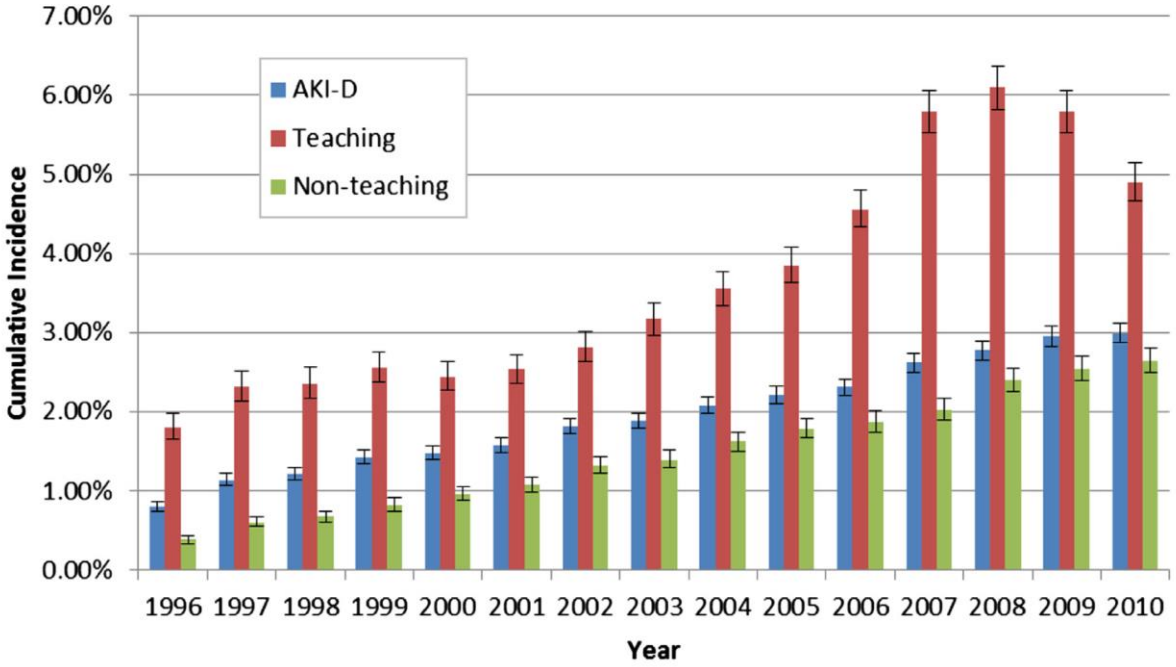
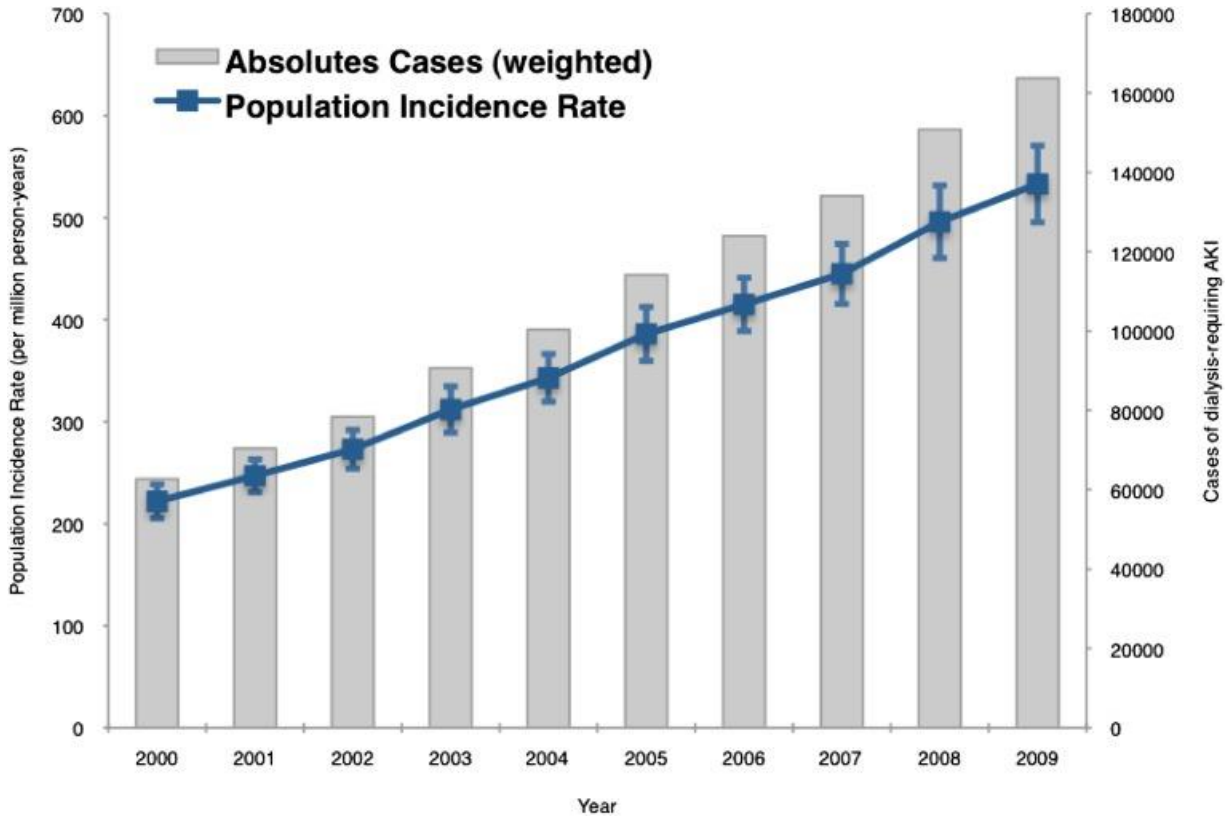


Temporal Changes in Incidence of Dialysis-Requiring AKI

Raymond K. Hsu,* Charles E. McCulloch,† R. Adams Dudley,* Lowell J. Lo,* and Chi-yuan Hsu*



Temporal trends for increased RRT utilization for critically ill patients with AKI

Wald et al AJKD 2014; Hsu et al JASN 2013

THE LANCET

JANUARY 21, 1961

OPTIMUM TIME FOR DIALYSIS IN ACUTE REVERSIBLE RENAL FAILURE

Description and Value of an Improved Dialyser with Large Surface Area

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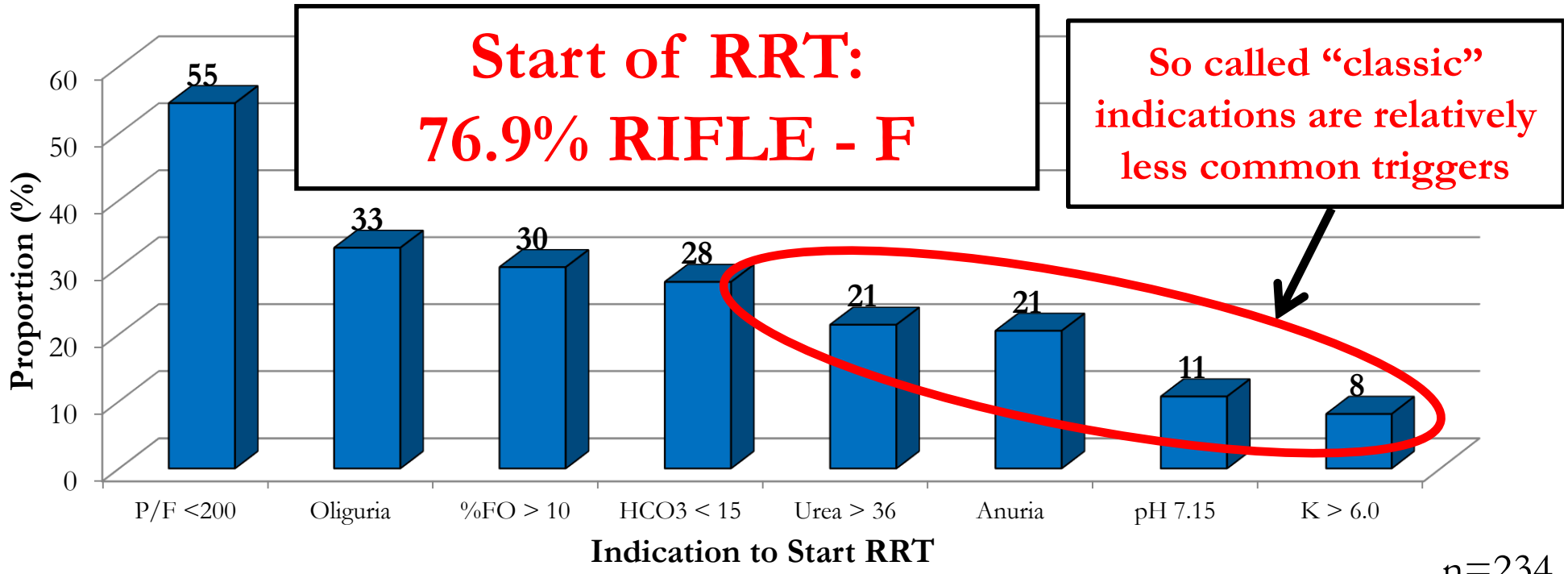
From the General Infirmary at Leeds

"Classic" or "Conventional" Indications for Starting RRT

Oligo-anuria	Urine output <200mL/12 hr or anuria
Azotemia	Urea>36 mmol/L or uremic organ complications
Hyperkalemia	K+ >6.5 and/or rapidly rising and/or ECG abnormalities
Metabolic acidosis	pH <7.15
Sodium disorders	Progressive and/or uncontrolled hypo/hypernatremia
Thermoregulation	Uncontrolled hyperthermia and/or hypothermia (>39.5 C)
Volume overload	Clinically significant, diuretic-unresponsive organ edema
Overdose	Drug overdose with dialyzable toxin

Clinical factors associated with initiation of renal replacement therapy in critically ill patients with acute kidney injury—A prospective multicenter observational study ☆

Sean M. Bagshaw [a,*,1], Ron Wald [c,1], Jim Barton [b,1], Karen E.A. Burns [c,1], Jan O. Friedrich [c,1], Andrew A. House [d,1], Matthew T. James [e,1], Adeera Levin [g,1], Louise Moist [d,1], Neesh Pannu [a,1], Daniel E. Stollery [h,1], Michael W. Walsh [e,f,1]



n=234

Bagshaw et al J Crit Care 2011

KDIGO CLINICAL PRACTICE GUIDELINE FOR ACUTE KIDNEY INJURY

- **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)

Earlier Start to RRT in AKI

Benefits

- Azotemic control
- Electrolyte/acid-base homeostasis
- Fluid balance homeostasis
- Prevent complications of AKI
- Immunomodulation?

Risks

- CVC insertion
- Extracorporeal circuit
- Anticoagulation
- Micronutrient depletion
- Added bedside resources
- Impaired/disrupted recovery*

Balance of decision to start based on indications and perception of whether of there will be greater benefit relative to potential harm

- Decision to start is largely <u>subjective</u> based on the spectrum of clinical information and provider bias:
  - Providers start when confronted with "life-threatening" complications
  - Wide variation in the "minimum" severity of indications prompting start of RRT
  - Many factors modify the decision: age, comorbidity, responsiveness to a diuretic challenge, illness severity (predicted mortality), prescribing service, time of day, day of week

Timing of Renal Replacement Therapy and Patient Outcomes in the Randomized Evaluation of Normal Versus Augmented Level of Replacement Therapy Study*

Min Jun, MScMed(ClinEpi), PhD[1]; Rinaldo Bellomo, MBBS, MD[2]; Alan Cass, MBBS, PhD[1,3]; Martin Gallagher, MBBS, PhD[1]; Serigne Lo, MSc, PhD[1]; Joanne Lee, BMedSc (Hons)[1]; for the Randomized Evaluation of Normal Versus Augmented Level of Replacement Therapy (RENAL) Study Investigators

Objectives: To explore the relationship between timing of continuous renal replacement therapy commencement and clinical outcomes in critically ill patients with acute kidney injury. The primary outcomes were all-cause mortality at 28 and 90 days.

Design: Nested observational cohort study using data from the Randomized Evaluation of Normal Versus Augmented Level Replacement Therapy Study.

Setting: Twenty-three ICUs in Australia and New Zealand.

Patients: Four hundred thirty-nine critically ill patients with acute kidney injury Risk, Injury, Failure, Loss, End-stage kidney disease-injury (RIFLE-I) criteria.

Interventions: None.

Measurements and Main Results: The time between RIFLE-I acute kidney injury and randomization in the Randomized Evaluation of Normal Versus Augmented Level Replacement Therapy Study (proxy for continuous renal replacement therapy commencement) was the variable of interest. All baseline variables in the Randomized Evaluation of Normal Versus Augmented Level Replacement Therapy Study were assessed. Multivariable Cox, logistic, and linear regression models were used to assess the independent relationship of time of onset of RIFLE-I acute kidney injury and randomization and patient outcomes. The median time between RIFLE-I acute kidney injury and continuous renal replacement therapy commencement was 17.6 hours (interquartile range, 7.1–46 hr). Based on four groups of continuous renal replacement therapy commencement ([group 1; reference]: < 7.1, [group 2]: ≥ 7.1 to < 17.6, [group 3]: ≥ 17.6 to < 46.0, [group 4]: ≥ 46.0 hr), earlier commencement of continuous renal replacement therapy was not associated with a significantly lower risk of death at 28 days (hazard ratio for group 2: 1.06, 95% CI: 0.62–1.81; $p = 0.83$; hazard ratio for group 3: 1.23, 95% CI: 0.71–2.12; $p = 0.46$; hazard ratio for group 4: 1.33, 95% CI: 0.77–2.31; $p = 0.31$). Similar findings were observed for death at 90 days.

Conclusions: In a subgroup of participants of the Randomized Evaluation of Normal Versus Augmented Level Replacement Therapy Study, earlier commencement of continuous renal replacement therapy relative to RIFLE-I acute kidney injury was not

*See also p. 1933.

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The Randomized Evaluation of Normal Versus Augmented Level of Replacement Therapy (RENAL) Study Investigators are listed in **Appendix 1**.

Dr. Jun was responsible for data collection, analysis, interpretation, and article preparation. Drs. Bellomo, Cass, Gallagher, and Lo contributed to study concept design. All authors contributed to data interpretation and critical review of the article. Dr. Bellomo had full access to all data in the study and takes responsibility for the integrity of the data and accuracy of the analysis.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccmjournal).

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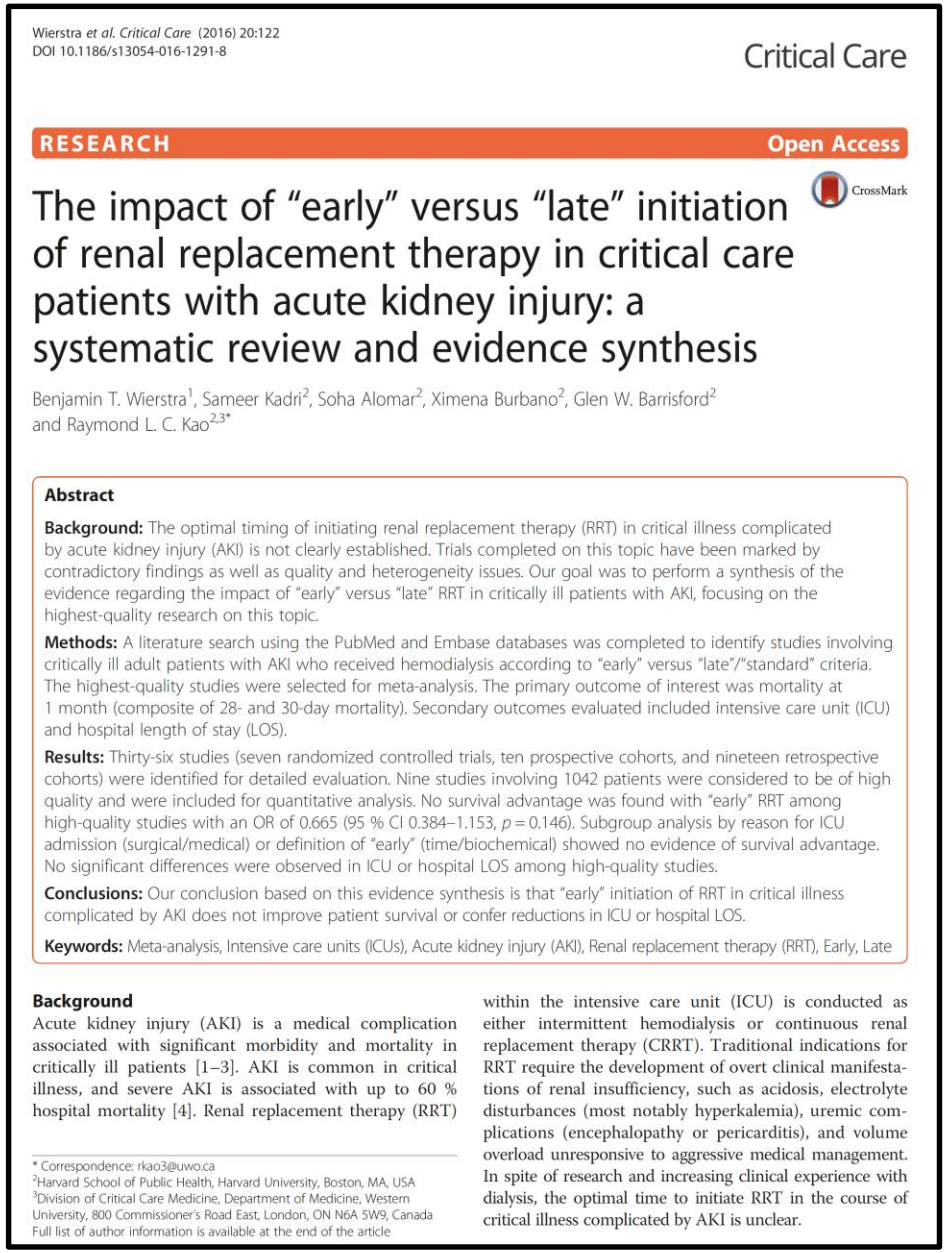

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Critical Care

RESEARCH Open Access

The impact of "early" versus "late" initiation of renal replacement therapy in critical care patients with acute kidney injury: a systematic review and evidence synthesis

Benjamin T. Wierstra[1], Sameer Kadri[2], Soha Alomar[2], Ximena Burbano[2], Glen W. Barrisford[2] and Raymond L. C. Kao[2,3*]

Abstract

Background: The optimal timing of initiating renal replacement therapy (RRT) in critical illness complicated by acute kidney injury (AKI) is not clearly established. Trials completed on this topic have been marked by contradictory findings as well as quality and heterogeneity issues. Our goal was to perform a synthesis of the evidence regarding the impact of "early" versus "late" RRT in critically ill patients with AKI, focusing on the highest-quality research on this topic.

Methods: A literature search using the PubMed and Embase databases was completed to identify studies involving critically ill adult patients with AKI who received hemodialysis according to "early" versus "late"/"standard" criteria. The highest-quality studies were selected for meta-analysis. The primary outcome of interest was mortality at 1 month (composite of 28- and 30-day mortality). Secondary outcomes evaluated included intensive care unit (ICU) and hospital length of stay (LOS).

Results: Thirty-six studies (seven randomized controlled trials, ten prospective cohorts, and nineteen retrospective cohorts) were identified for detailed evaluation. Nine studies involving 1042 patients were considered to be of high quality and were included for quantitative analysis. No survival advantage was found with "early" RRT among high-quality studies with an OR of 0.665 (95 % CI 0.384–1.153, $p = 0.146$). Subgroup analysis by reason for ICU admission (surgical/medical) or definition of "early" (time/biochemical) showed no evidence of survival advantage. No significant differences were observed in ICU or hospital LOS among high-quality studies.

Conclusions: Our conclusion based on this evidence synthesis is that "early" initiation of RRT in critical illness complicated by AKI does not improve patient survival or confer reductions in ICU or hospital LOS.

Keywords: Meta-analysis, Intensive care units (ICUs), Acute kidney injury (AKI), Renal replacement therapy (RRT), Early, Late

Background

Acute kidney injury (AKI) is a medical complication associated with significant morbidity and mortality in critically ill patients [1–3]. AKI is common in critical illness, and severe AKI is associated with up to 60 % hospital mortality [4]. Renal replacement therapy (RRT) within the intensive care unit (ICU) is conducted as either intermittent hemodialysis or continuous renal replacement therapy (CRRT). Traditional indications for RRT require the development of overt clinical manifestations of renal insufficiency, such as acidosis, electrolyte disturbances (most notably hyperkalemia), uremic complications (encephalopathy or pericarditis), and volume overload unresponsive to aggressive medical management. In spite of research and increasing clinical experience with dialysis, the optimal time to initiate RRT in the course of critical illness complicated by AKI is unclear.

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- "Our conclusion based on this evidence synthesis [*36 studies – 7 randomized controlled trials*] is that "early" initiation of RRT [*however defined*] in critical illness complicated by AKI does not improve survival or confer reductions in ICU or hospital LOS."

Effects of early high-volume continuous venovenous hemofiltration on survival and recovery of renal function in intensive care patients with acute renal failure: A prospective, randomized trial

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Objective: To study the effects of the initiation time of continuous venovenous hemofiltration and of the ultrafiltrate rate in patients with circulatory and respiratory insufficiency developing early oliguric acute renal failure. The primary end points were mortality at 28 days and recovery of renal function.

Design: A randomized, controlled, two-center study.

Setting: The closed-format multidisciplinary intensive care units of a university hospital (30 beds) and a teaching hospital (18 beds).

Patients and Interventions: A total of 106 ventilated severely ill patients who were oliguric despite massive fluid resuscitation, inotropic support, and high-dose intravenous diuretics were randomized into three groups. Thirty-five patients were treated with early high-volume hemofiltration (72–96 L per 24 hrs), 35 patients with early low-volume hemofiltration (24–36 L per 24 hrs), and 36 patients with late low-volume hemofiltration (24–36 L per 24 hrs).

Results: Median ultrafiltrate rate was 48.2 (42.3–58.7) $mL \cdot kg^{-1} \cdot hr^{-1}$ in early high-volume hemofiltration, 20.1 (17.5–22.0) $mL \cdot kg^{-1} \cdot hr^{-1}$ in early low-volume hemofiltration, and 19.0 (16.6–21.1) $mL \cdot kg^{-1} \cdot hr^{-1}$ in late low-volume hemofiltration. Survival at day 28 was 74.3% in early high-volume hemofiltration, 68.8% in early low-volume hemofiltration, and 75.0% in late low-volume hemofiltration ($p = .80$). On average, hemofiltration started 7 hrs after inclusion in the early groups and 42 hrs after inclusion in the late group. All hospital survivors had recovery of renal function at hospital discharge, except for one patient in the early low-volume hemofiltration group. Median duration of renal failure in hospital survivors was 4.3 (1.4–7.8) days in early high-volume hemofiltration, 3.2 (2.4–5.4) days in early low-volume hemofiltration, and 5.6 (3.1–8.5) days in late low-volume hemofiltration ($p = .25$).

Conclusions: In the present study of critically ill patients with oliguric acute renal failure, survival at 28 days and recovery of renal function were not improved using high ultrafiltrate volumes or early initiation of hemofiltration. (Crit Care Med 2002; 30:2205–2211)

KEY WORDS: hemofiltration; acute renal failure; survival; ultrafiltrate; mechanical ventilation; shock; oliguria

Oliguric acute renal failure (ARF) is a frequent complication in patients with septic or cardiogenic shock. Pending recovery of renal function, temporary renal replacement therapy is required in most cases. In daily practice, there is substantial variation in the policies regarding initiation time of renal replacement therapy and in the way it is performed. Apart from intermittent hemodialysis, other techniques, including peritoneal dialysis, continuous arteriovenous hemo(dia)filtration, and continuous venovenous hemo(dia)filtration, are being used. It is generally accepted that in intensive care patients with ARF, the continuous techniques are superior to intermittent hemodialysis, in particular with respect to hemodynamic stability (1, 2). Despite the implementation of continuous techniques, patient outcome is still very poor. Most studies of ARF in intensive care patients reported a mortality between 60% and 80% (3–6). Low clearance techniques were used in these studies, and renal replacement was started late in the course of renal failure. Nonrandomized studies suggest that both earlier initiation of renal replacement therapy and the use of higher ultrafiltrate rates might improve survival and recovery of renal function (7, 8). In a recent prospective randomized study, improvement of survival was reported by increasing the ultrafiltrate rate (9). The aim of the present study was to evaluate the effects of initiation time of hemofiltration and of ultrafiltrate rate in patients with circulatory and respiratory insufficiency and early ARF. The primary end points were mortality at 28 days and recovery of renal function.

METHODS

The study was designed as a randomized trial comparing three treatment strategies: early high-volume hemofiltration (EHV), early low-volume hemofiltration (ELV), and late low-volume hemofiltration (LLV). The Academic Medical Center, a university hospital with a 30-bed closed-format multidisciplinary intensive care unit (ICU), and the Onze Lieve Vrouwe Gasthuis, a teaching hospital with an 18-bed closed-format multidisciplinary ICU, participated in the study. Both centers prac-

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AJKD

Original Investigation

Earlier-Start Versus Usual-Start Dialysis in Patients With Community-Acquired Acute Kidney Injury: A Randomized Controlled Trial

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Background: Optimum timing of the initiation of dialysis therapy in acute kidney injury is not clear.

Study Design: Prospective, open label, 2-arm, randomized, controlled trial.

Setting & Participants: 208 adults with acute kidney injury with progressively worsening azotemia at the artificial kidney dialysis unit of a tertiary-care referral center in western India.

Intervention: Earlier-start dialysis was initiated when serum urea nitrogen and/or creatinine levels increased to 70 and 7 mg/dL, respectively, whereas the usual-start dialysis patients (control group) received dialysis when clinically indicated as judged by treating nephrologists.

Outcomes: Primary outcome was in-hospital mortality and dialysis dependence at 3 months. Secondary outcome in patients receiving dialysis was time to recovery of kidney function, computed from time of enrollment to the last dialysis session.

Results: Of 585 screened patients, 102 were assigned to earlier-start dialysis, and 106 to usual-start dialysis. Baseline characteristics were similar between randomized groups. 93 (91.1%) and 88 (83.1%) participants received dialysis in the intervention and control groups, respectively. Mean serum urea nitrogen and serum creatinine levels at dialysis therapy initiation were 71.7 ± 21.7 (SD) and 7.4 ± 5.3 mg/dL, respectively, in the intervention group versus 100.9 ± 32.6 and 10.41 ± 3.3 mg/dL in the control group. Data on primary outcome were available for all patients. In-hospital mortality was 20.5% and 12.2% in the intervention and control groups, respectively (relative risk, 1.67; 95% CI, 0.88-3.17; $P = 0.2$). 4.9% and 4.7% of patients in the intervention and control groups, respectively, were dialysis dependent at 3 months (relative risk, 1.04; 95% CI, 0.29-3.7; $P = 0.9$).

Limitations: Study was not double blind, event rate (ie, mortality) was less than predicted, wide CIs preclude definitive findings.

Conclusions: Our data do not support the earlier initiation of dialysis therapy in community-acquired acute kidney injury.

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INDEX WORDS: Acute kidney injury; dialysis start; mortality; dialysis dependence.

Editorial, p. 1030

Acute kidney injury (AKI) is present in 5% of hospitalized patients and is associated with high mortality (range, 20%-60%).[1-3] More than 200 years after AKI was first described as "ischuria renalis" by William Heberden,[4] therapy to alter the natural course of tubular injury remains elusive and treatment is mainly supportive. Dialysis is required in some of these patients to treat various complications of AKI before kidneys recover. Data for the optimum time to start dialysis therapy are lacking and are considered as one of the top research priorities in AKI.[5,6] Systematic reviews and meta-analyses addressing this issue have concluded that available data are inconclusive and have suggested the need for a randomized controlled trial on the correct timing of dialysis therapy initiation.[5,7,8]

Available research on the treatment of AKI is related principally to critically ill patients in intensive care unit settings. Community-acquired AKI is the most common renal emergency in developing countries and contributes to one-third of the global AKI burden.[9] In contrast to sepsis-associated AKI in the critically ill, community-acquired AKI is characterized by younger age of the affected population, less severe extrarenal organ dysfunction, lower comorbid condition burden, and an overall better outcome.[9,10]

In the absence of data from prospective trials, practice regarding the initiation of dialysis therapy in AKI varies widely and dialysis before the onset of overt complications of kidney failure often is used. Whether earlier initiation of dialysis therapy improves survival in AKI is not known. A single prospective randomized

From the Seth GS Medical College and KEM Hospital, Mumbai.

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0272-6386/$36.00

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Clinical Dilemma To Be Addressed

- The **optimal timing of RRT initiation** in critically ill patients with AKI is uncertain
- No consensus to guide clinical practice on this issue
- Wide variability in the timing of RRT initiation in this population
- This is an important knowledge gap in the support of critically ill patients with AKI

ORIGINAL ARTICLE

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

- **HYPOTHESIS:**
  - A strategy of **delayed RRT initiation** would confer **greater survival benefit** when compared to a strategy of early RRT initiation among critically ill patients with severe AKI (KDIGO stage 3)

Gaudry et al NEJM 2016

- **DESIGN:** Multi-centre, unblinded, parallel group, randomized trial
- **POPULATION:** 620 critically ill patients with AKI (KDIGO stage 3) with no absolute indication and supported with mechanical ventilation and/or vasoactive therapy
- **INTERVENTIONS (STRATEGIES):**
  - EARLY = RRT within 6 hr of fulfilling KDIGO stage 3 AKI (98% at 4.3 hr)
  - DELAYED = RRT in response to clinical criteria & complications (51% at 57 hr)

RRT delivery not protocolized and prescribed according to French guidelines (only criteria for starting)

(initial IHD in 55% ~ similar in both groups)

- **PRIMARY ENDPOINT:** Mortality at 60-days

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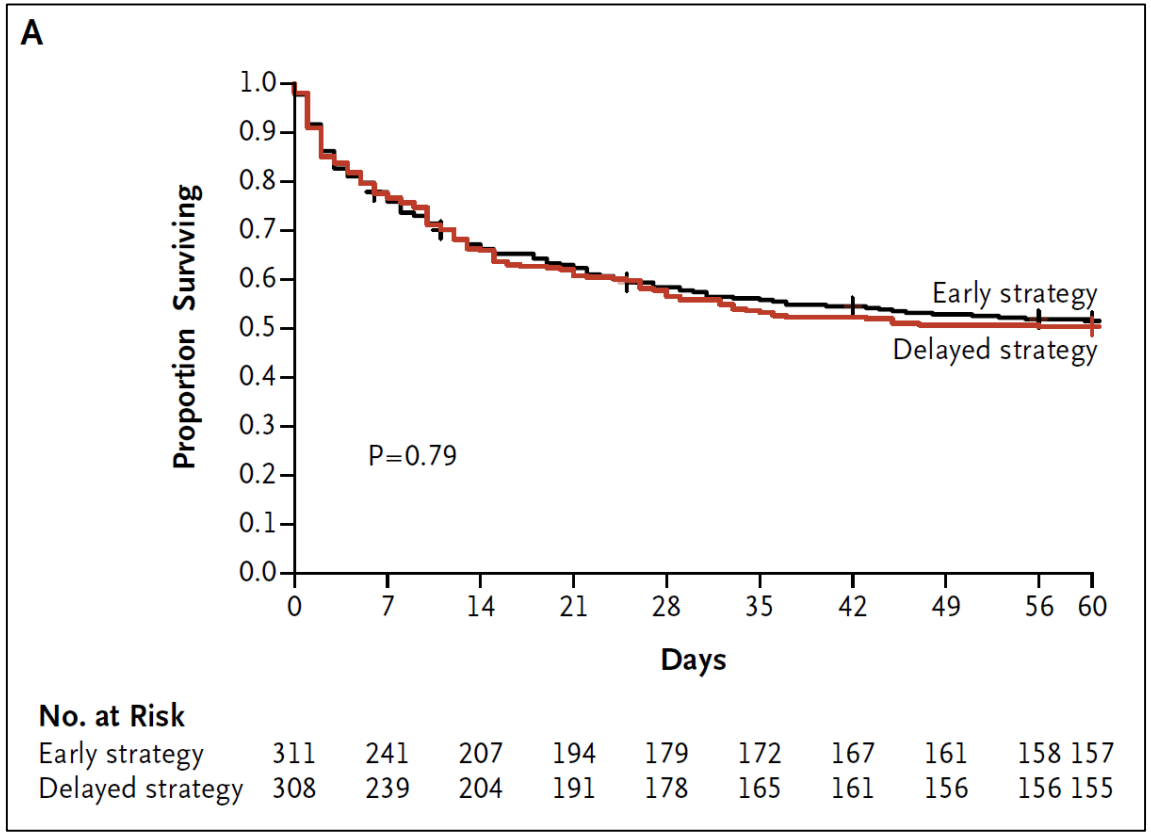
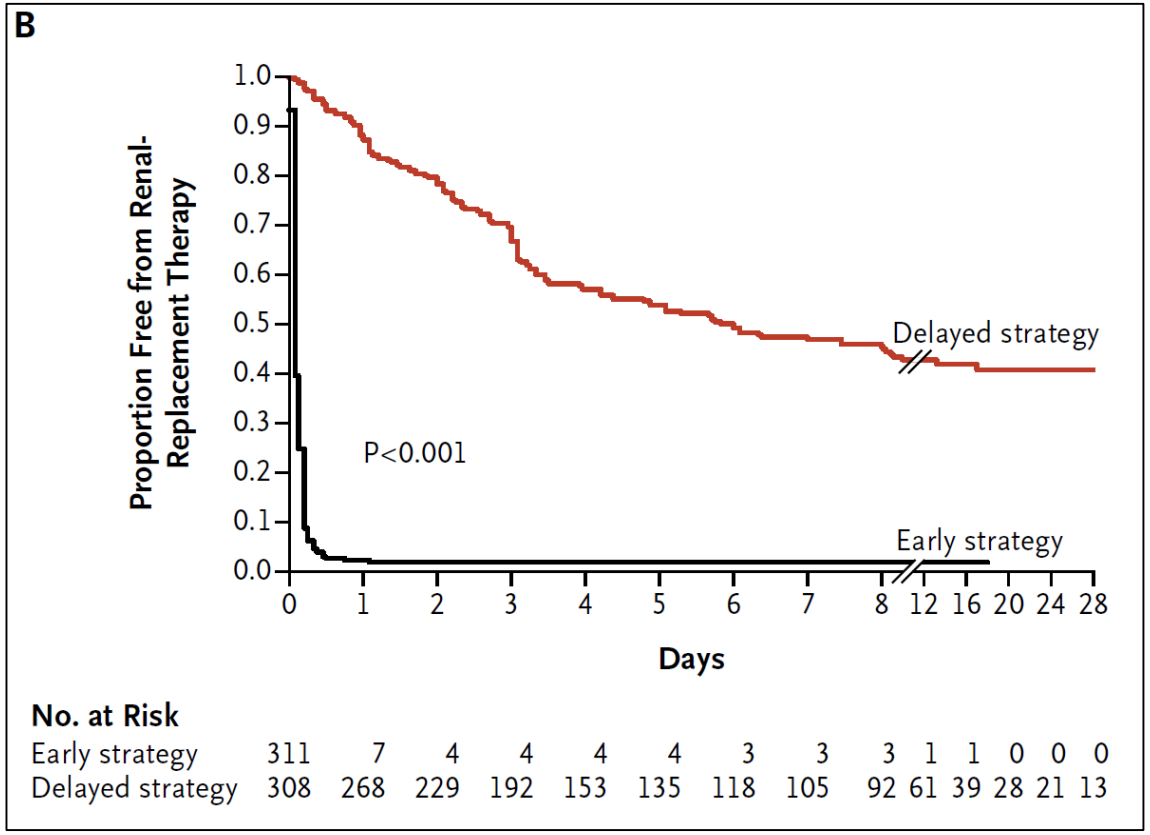
Survival at 60-days



RRT-free at 28-days



Mortality at 60-days: 48.5% vs. 49.7% (p=0.79)

Separation of ~ 57 hr (25-83) for starting RRT

49% of DELAYED group did not receive RRT (and ↓ CRBSI rate)

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Table S3. Distribution of criteria which mandated RRT initiation in the delayed strategy group* (157 patients of 308 in this group actually received RRT)	
Criteria	
Oliguria or anuria for more than 72 hours after randomization – no. (%)	59 (38)
Blood urea nitrogen of more than 112 md/dl (40 mmol/liter) – no. (%)	59 (38)
Serum potassium concentration of more than 6 mmol/liter or more than 5.5 mmol/liter despite medical treatment (bicarbonate and/or glucose-insulin infusion) – no. (%)	27 (17)
pH below 7.15 in a context of pure metabolic acidosis ($PaCO_2$<35 mmHg) or in a context of mixed acidosis with $PaCO_2$ of 50 mmHg or more without possibility of increasing alveolar ventilation – no. (%)	33 (21)
Acute pulmonary edema due to fluid overload leading to severe hypoxemia requiring oxygen flow rate of more than 5 l/min to maintain SpO_2 of more than 95% or requiring an FiO_2 greater than 50% in patients already on invasive or non-invasive mechanical ventilation and despite diuretic therapy – no. (%)	9 (6)
Others	5 (3)

DELAYED RRT CRITERIA

Key triggers for RRT initiation were: oliguria ≥ 72 hr, and serum urea ≥ 40 mmol/L

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Table S4. Patient characteristics at the time of RRT initiation *

Characteristic	Early RRT strategy N=305 †	Delayed RRT strategy N=157	P Value
Urine output before RRT – ml/24h –median (IQR) ‡	—	150 (50-600)	
Serum creatinine – mg/dl	3.27±1.37	5.33±2.33	<0.001
Blood urea nitrogen – mg/dl	52±24	90±34	<0.001
Potassium – mmol/liter	4.4±0.7	5.1±0.9	<0.001
Bicarbonate – mmol/liter	18.9±4.9	16.6±5.6	<0.001
pH	7.30±0.12	7.25±0.15	<0.001
Sodium – mmol/liter	137.9±5.9	137.3±6.2	0.26
Invasive mechanical ventilation – no. (%)	264 (87)	138 (88)	0.75
Vasopressor (epinephrine or norepinephrine) support – no. (%)	254 (84)	125 (80)	0.30
Epinephrine dose – mg/hour	2.8±2.1	6.1±5.5	0.14
Norepinephrine dose – mg/ hour	4.2±4.2	5.6±7.5	0.57

Did a protocol-mandated delay in starting RRT contribute to undesirable events?

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DELAYED >> EARLY: accumulated metabolic complications and were exposed to interventions to manage AKI complications

Table S7. Medical treatment of AKI-related metabolic complication before the first RRT session for patients who received it or during the whole ICU stay for patients who did not receive it

Characteristic	Early RRT strategy n=311	Delayed RRT strategy n=308	P Value
Diuretics– no. (%)	4 (1.3)	112 (36.5)	<0.001
Medical treatment of hyperkalemia – no. (%)	17 (5.5%)	67 (22.9%)	<0.001
Medical treatment of acidosis– no. (%)	21 (6.8%)	49 (16.7%)	<0.001

Was there an association between these complications and the observed deleterious outcome of receiving RRT?

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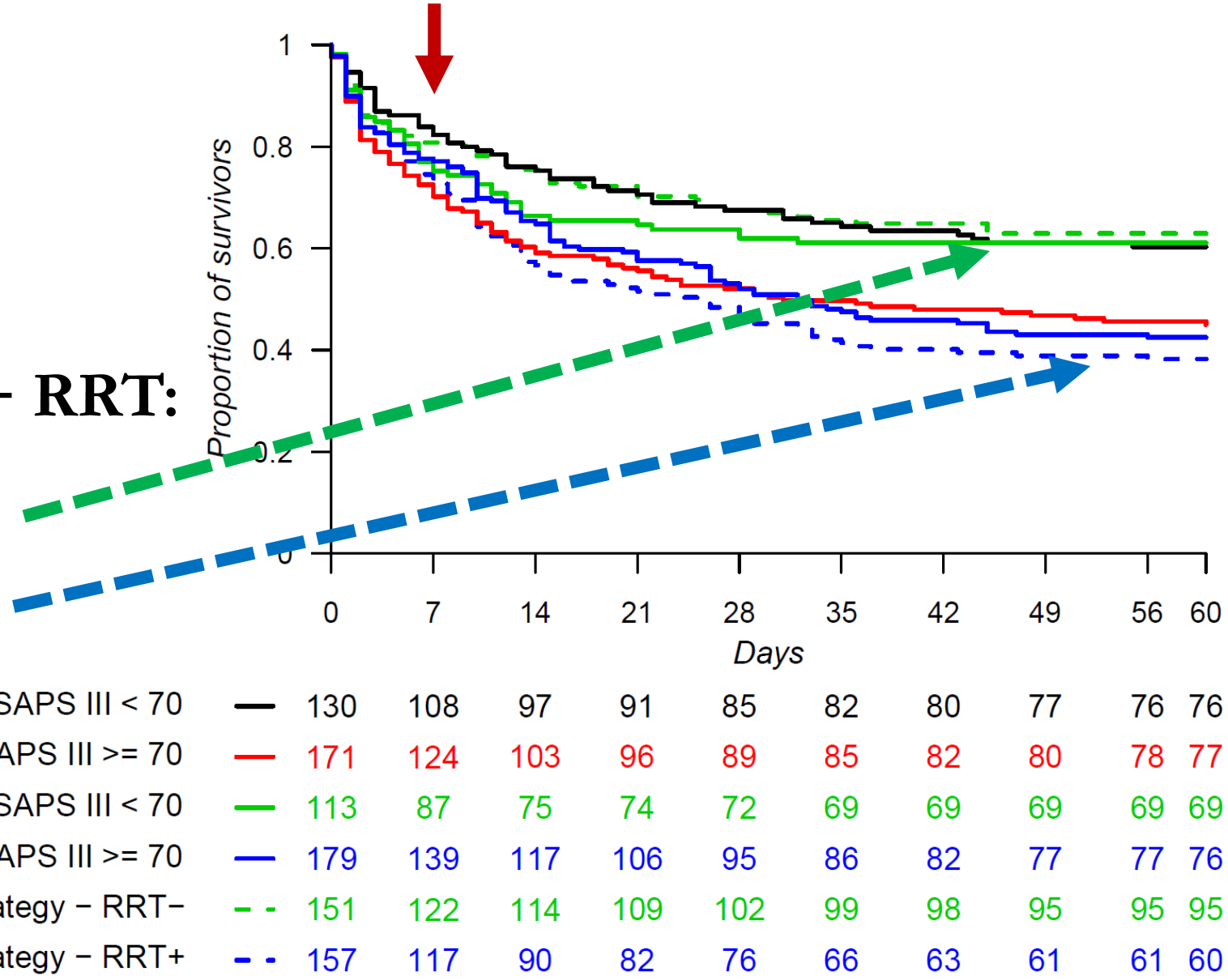
- **DELAYED >> EARLY:**
- ↑ CKD (12% vs. 7%, p=0.02)
- ↑ bleeding complications
- ↑ RRT sessions among survivors

- **Death modified by acuity + RRT:**
  - Early: 48.5%
  - Delayed – NO RRT: 37.1%
  - Delayed – RRT: 61.8%



Gaudry et al NEJM 2016

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

- **DESIGN:** Single-centre, unblinded, parallel group, randomized clinical trial
- **POPULATION:** 231 critically ill patients with AKI (KDIGO stage 2) + pNGAL > 150 ng/mL + one of (sepsis; vasoactives; refractory FO; worsening SOFA)
- **INTERVENTIONS (stratified by SOFA + oliguria):**
  - EARLY = RRT within 8 hr of KDIGO stage 2
  - DELAYED = RRT within 12 hr of KDIGO stage 3
- **PRIMARY ENDPOINT:** Mortality at 90-days

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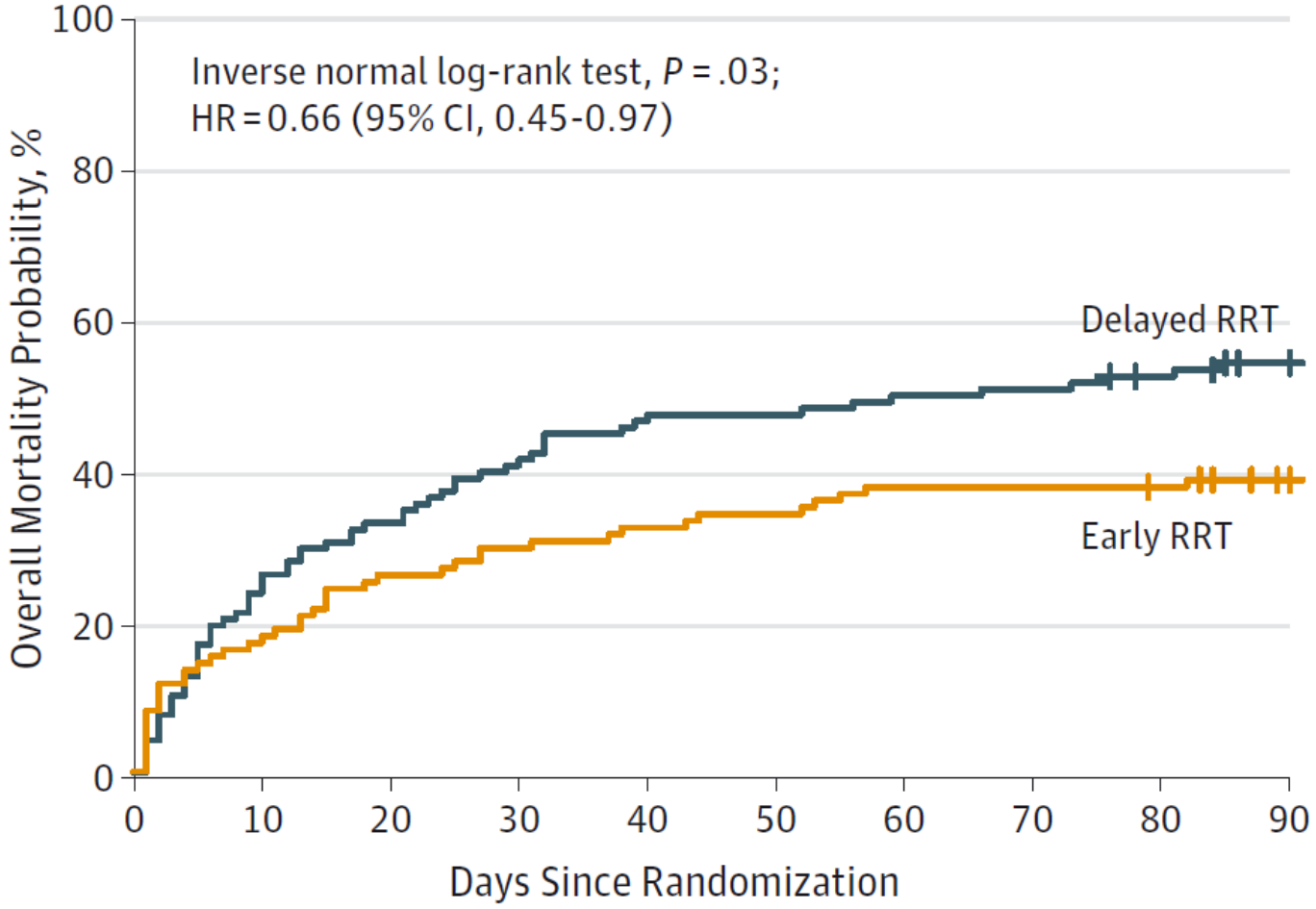

No. at risk

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

Mortality at 90-days:

EARLY 39.3%

vs

DELAYED 53.6%

(ARR -15.4%)

(HR 0.66, 0.45-0.97)

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- **EARLY >> DELAYED RRT** contributed to:
  - ↓ RRT duration (9 d vs. 25 d; **-18 days**; p=0.04)
  - ↑ kidney recovery (53.6% vs. 38.7%, **+14.9%**, p=0.02), *but not after excluding deaths through 90 days (p=0.62)*
  - ↓ MV duration (125 hr vs. 181 hr; **-60 hr**; p=0.002)
  - No difference in ICU stay
  - ↓ hospital stay (among survivors to 90-days) (51 vs. 82 d; **-37 days**; p<0.01)

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		Early, d0 (n=112)	Delayed, d0 (n=119)	Absolute difference Early - Delayed [95% CI]	p-value	Early, d1 (n=112)	Delayed, d1 (n=119)	Absolute difference Early - Delayed [95% CI]	p-value
MIF, (Q1, pg/ml	median Q3),	18471.6 (8423.4, 48146.4)	16675.2 (10155.6, 38407.2)	-98.4 [-4465.2, 4647.6]	0.79	14388.0 (6393.3, 28118.7)	15346.2 (7362.9, 30125.7)	-1132.2 [-4747.2, 2564.4]	0.89
IL-6, (Q1, pg/ml	median Q3),	1218.3 (435.6, 2142.0)	871.1 (217.5, 1778.4)	224.9 [30.4, 467.9]	0.41	399.4 (116. 5, 901.1)	989.3 (190.9, 2012.8)	-310.9 [-663.2, -93.3]	**0.02**
IL-8, (Q1, pg/ml	median Q3),	344.0 (145.5, 568.1)	222.6 (71.8, 480.5)	73.0 [10.4, 143.5]	0.08	65.7 (28.0, 162.5)	215.5 (67.3, 373.7)	-105.9 [-160.6, -52.7]	**0.001**
IL-18, (Q1, pg/ml	median Q3),	552.1 (270.7, 1137.7)	605.6 (309.7, 1386.1)	-49.4 [-178.8, 77.3]	0.46	518.4 (351.0, 1056.8)	603.9 (316.0, 1379.8)	-27.3 [-185.3, 101.9]	0.28
IL-10, (Q1, pg/ml	median Q3),	51.6 (20.2, 211.2)	45.0 (17.2, 159.9)	3.9 [-7.9, 19.0]	0.68	27.0 (12.4, 73.1)	30.7 (13.0, 67.5)	-0.9 [-9.0, 6.5]	0.72

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ELAIN: Additional Considerations….

- **POPULATION:** mostly surgical (46.7% cardiac surgical)
- **ELIGIBILITY:** NGAL > 150 excluded only 3/604 patients
- **DELAYED:** Nearly all worsened ~ only 9.2% did not receive RRT
- **DELAYED:** "absolute indication" in only 15.1%
- **PRIMARY OUTCOME:** Observed effect implausibly large and "*likely inflated*" as suggested by the authors (Fragility Index 3)

Zarbock et al JAMA 2015

STARRT-AKI Research Program

- The over-arching question proposed is:

Does accelerated (or pre-emptive) initiation of RRT in critically ill patients with AKI, as compared to a conservative strategy to initiating RRT, reduce 90-day all-cause mortality and non-recovery of kidney function?

http://www.kidney-international.org clinical trial

see commentary on page 670

Comparison of standard and accelerated initiation of renal replacement therapy in acute kidney injury

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In patients with severe acute kidney injury (AKI) but no urgent indication for renal replacement therapy (RRT), the optimal time to initiate RRT remains controversial. While starting RRT preemptively may have benefits, this may expose patients to unnecessary RRT. To study this, we conducted a 12-center open-label pilot trial of critically ill adults with volume replete severe AKI. Patients were randomized to accelerated (12 h or less from eligibility) or standard RRT initiation. Outcomes were adherence to protocol-defined time windows for RRT initiation (primary), proportion of eligible patients enrolled, follow-up to 90 days, and safety in 101 fully eligible patients (57 with sepsis) with a mean age of 63 years. Median serum creatinine and urine output at enrollment were 268 micromoles/l and 356 ml per 24 h, respectively. In the accelerated arm, all patients commenced RRT and 45/48 did so within 12 h from eligibility (median 7.4 h). In the standard arm, 33 patients started RRT at a median of 31.6 h from eligibility, of which 19 did not receive RRT (6 died and 13 recovered kidney function). Clinical outcomes were available for all patients at 90 days following enrollment, with mortality 38% in the accelerated and 37% in the standard arm. Two surviving patients, both randomized to standard RRT initiation, were still RRT dependent at day 90. No safety signal was evident in either arm. Our findings can inform the design of a large-scale effectiveness randomized control trial.

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KEYWORDS: acute kidney injury; randomized controlled trial; renal replacement therapy

There is considerable uncertainty regarding the optimal timing of renal replacement therapy (RRT) initiation in critically ill patients with acute kidney injury (AKI).[1] Although the need to initiate RRT is unequivocal in patients with life-threatening AKI and complications that are refractory to medical measures, the advantages of commencing RRT in the absence of such complications are debatable. Earlier initiation of RRT may confer benefit through accelerated achievement of euvolemia, removal of toxic solutes, achievement of acid-base homeostasis, and prevention of overt complications attributable to AKI. On the other hand, spontaneous recovery of kidney function may occur in selected patients with severe AKI. Earlier initiation in these patients unnecessarily exposes them to the potential harms of vascular access (for example, hemorrhage, thrombosis, bacteremia) and the complications of RRT (for example, intradialytic hypotension, hypersensitivity to the extracorporeal circuit, clearance of trace elements, and antibiotics) along with added resource utilization.

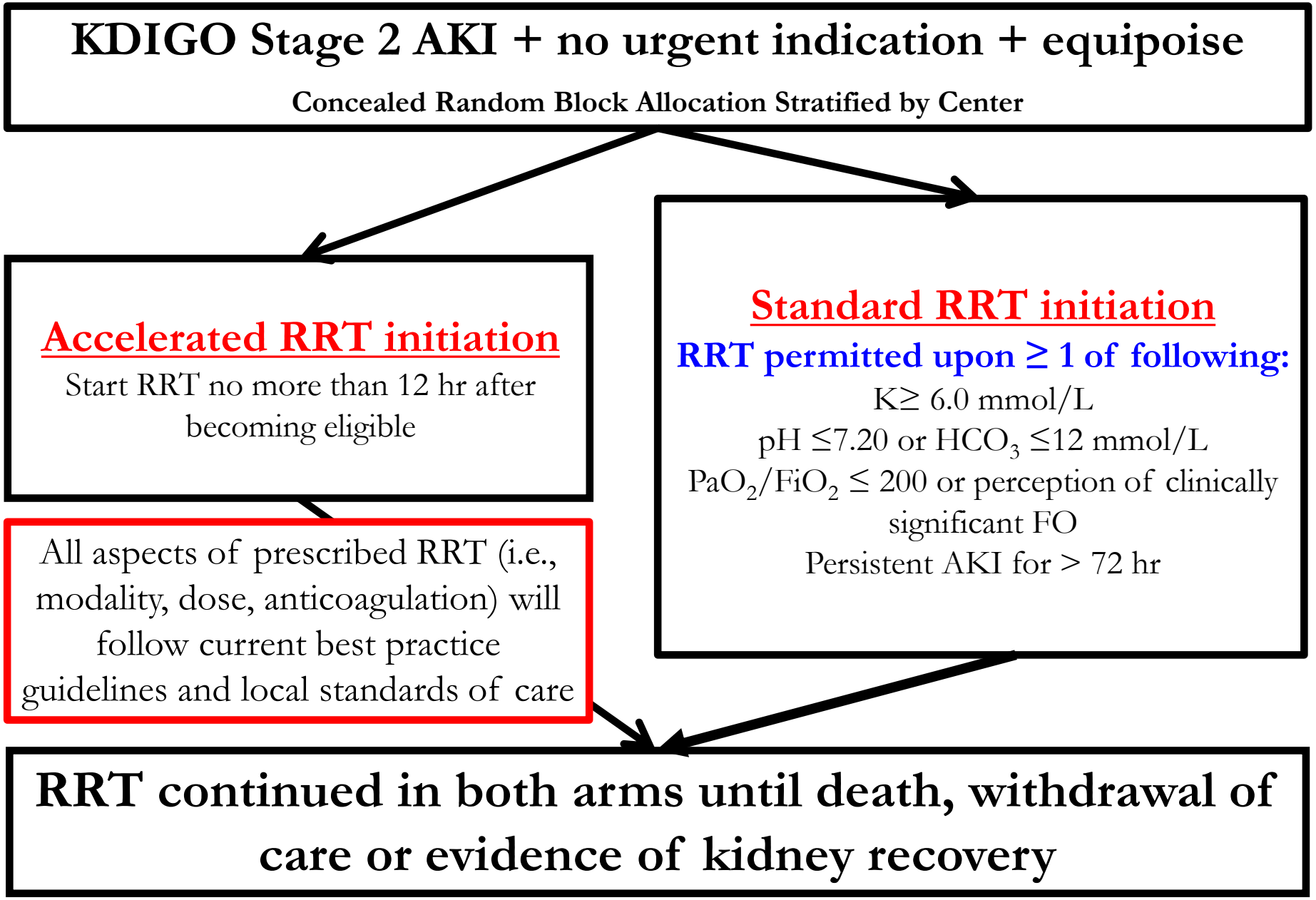
STARRT-AKI Pilot

- Multi-center, randomized, unblinded, pilot trial (n=100)
- 12 CCCTG-affiliated sites in Canada
- ICU patients with AKI and multi-organ support
- Feasibility of recruitment, protocol implementation and 90-day follow-up proven

Wald et al KI 2015

RRT Timing + Outcomes	Accelerated RRT (n=48)	Standard RRT (n=52)
Received RRT within 14 d (%)	48 (100)	33 (63)
Died or started RRT within 14 d (%)	48 (100)	39 (75)
Time from eligibility to RRT (mean), hr	9.7 ± 12.0	51.6 ± 52.0
Time from eligibility to RRT, (median), hr	7.4 (6.1-9.6)	31.6 (22.8-59.5)
90-Day mortality, (n, %)	18 (38)	19 (37)
RRT-dependent at 90-Days (n, %)	0 (0)	2 (6)
ICU stay among survivors, days	11 (8-29.5)	13.5 (8-32)
Hospital stay among survivors, days	29 (20-49)	31 (20-51)

Wald et al KI 2015


KDIGO Stage 2 AKI + no urgent indication + equipoise
Concealed Random Block Allocation Stratified by Center
Accelerated RRT initiation
Start RRT no more than 12 hr after becoming eligible
All aspects of prescribed RRT (i.e., modality, dose, anticoagulation) will follow current best practice guidelines and local standards of care
Standard RRT initiation
RRT permitted upon ≥ 1 of following:
K≥ 6.0 mmol/L
pH ≤7.20 or HCO_3 ≤12 mmol/L
PaO_2/FiO_2 ≤ 200 or perception of clinically significant FO
Persistent AKI for > 72 hr
RRT continued in both arms until death, withdrawal of care or evidence of kidney recovery

STARRT-AKI Trial Status (NCT02568722)

- **Active Sites:** 38 across 6 countries (another ~40 anticipated)
  - Canada, Australia, New Zealand, Finland, Ireland, United States
- **Randomized:** 260 (target 2,866 ~ 9.1% target)
- **Anticipated completion:** 2019

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Conclusions

- The issue of who, when and under what circumstance to ideally start RRT for critically ill patients with AKI (in the absence of life threatening complications) an important evidence care gap

- AKIKI/ELAIN have been major contributions towards improved understanding on this controversial issue ~ and has suggested that "waiting" may be an acceptable strategy

- Additional randomized trials are needed to harmonized AKIKI findings with other discordant trials

Thank You For Your Attention

Questions?

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George Institute	AHRC	CCCTG	ANZICS CTG
Judith Hall	Jane Holman		

University Hospital Foundation

CIHR IRSC Canadian Institutes of Health Research / Instituts de recherche en santé du Canada

CCCTG Canadian Critical Care Trials Group

AHRC Applied Health Research Centre

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Website: https://www.ualberta.ca/critical-care/research/current-research/starrtaki

Baxter

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