New and Emerging Evidence in the Delivery of Renal Replacement Therapy in AKI

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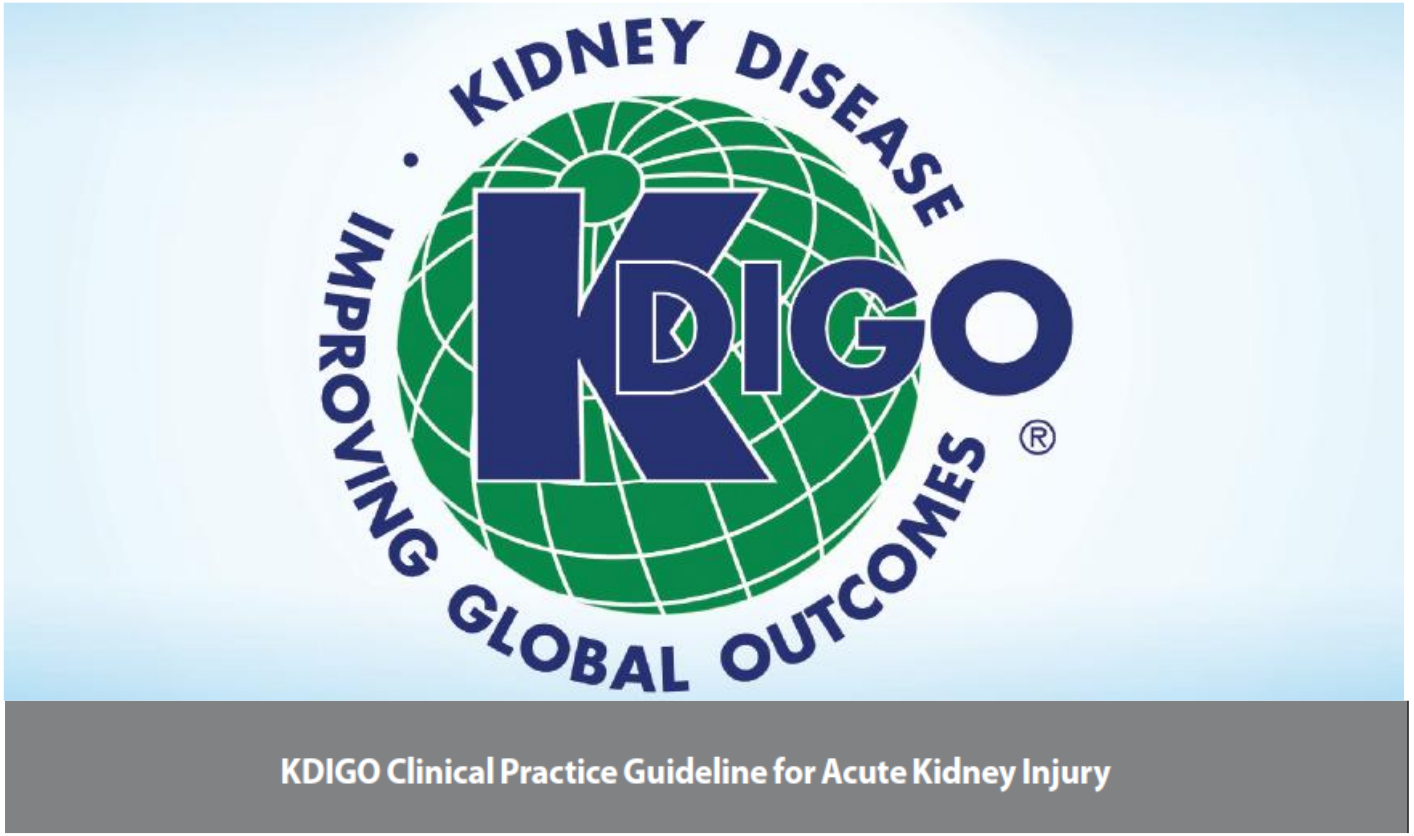
- Member, Scientific Committee, Canadian Society of Nephrology



Section 5: Dialysis Interventions for Treatment of AKI

Kidney International Supplements (2012) **2,** 89–115; doi:10.1038/kisup.2011.35

33 statements

14 were “suggestions”, 9 ungraded

Objective

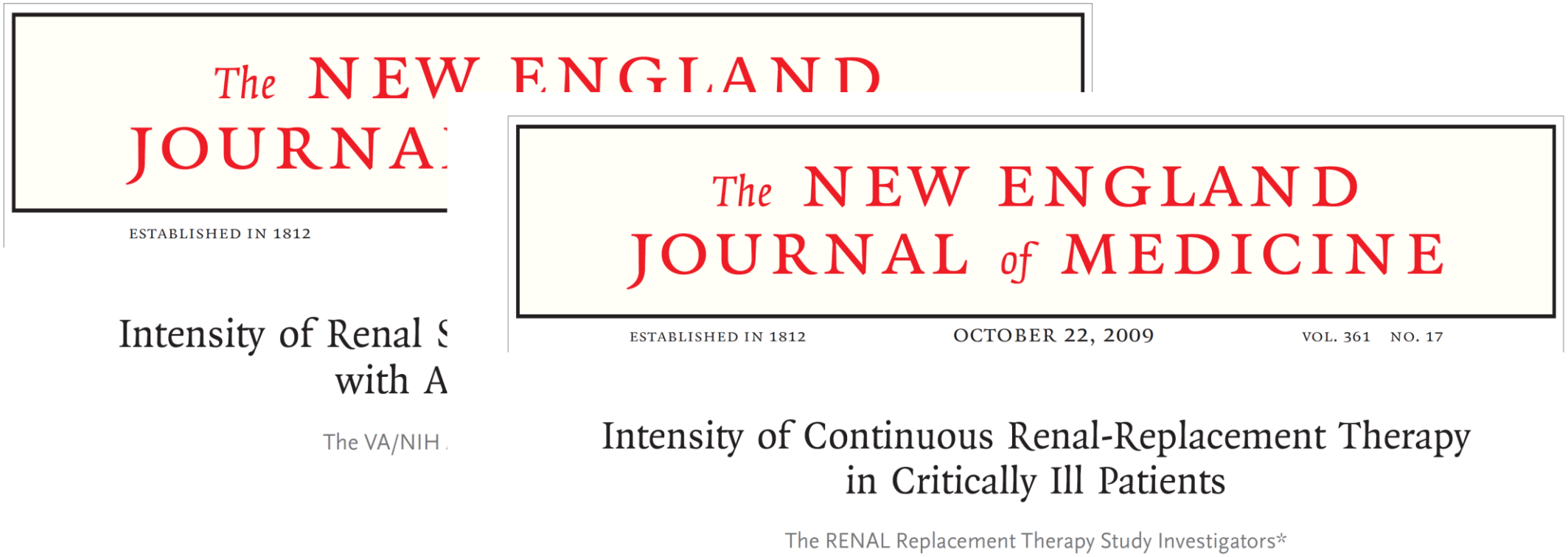
- To discuss three aspects of renal replacement therapy delivery where there is new and ongoing research
  - RRT dose
  - The RRT fluid prescription
  - RRT weaning/discontinuation

Revisiting the dose of CRRT

KDIGO Clinical Practice Guideline for Acute Kidney Injury

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*)

Where does this evidence come from?



The NEW ENGLAND JOURNAL

ESTABLISHED IN 1812

Intensity of Renal S
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The VA/NIH

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 22, 2009 VOL. 361 NO. 17

Intensity of Continuous Renal-Replacement Therapy in Critically Ill Patients

The RENAL Replacement Therapy Study Investigators*

Bottom line from these trials:

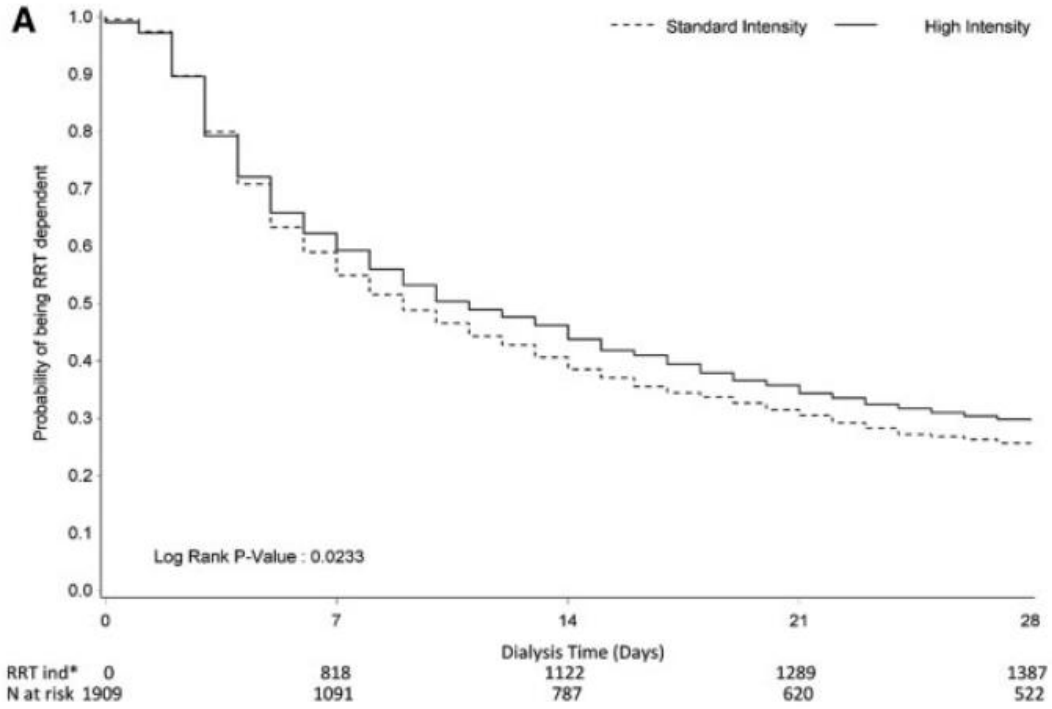
High-intensity CRRT (35-40 mL/kg/hr) did not mediate improved survival as compared to standard-intensity CRRT (20-25 mL/kg/hr)

Are there harms associated with higher intensity RRT?

- Compromise of therapeutic drug levels (especially antibiotics)
- Hypophosphatemia
- Loss of nutrients
- Persistent dialysis dependence?

Renal replacement therapy intensity for acute kidney injury and recovery to dialysis independence: a systematic review and individual patient data meta-analysis

Ying Wang[1,2], Martin Gallagher[1,2], Qiang Li[1], Serigne Lo[2,3], Alan Cass[4], Simon Finfer[1,2], John Myburgh[1,5], Catherine Bouman[6], Robert Faulhaber-Walter[7], John A Kellum[8], Paul M Palevsky[9], Claudio Ronco[10], Patrick Saudan[11], Ashita Tolwani[12] and Rinaldo Bellomo[1,13]



Higher intensity CRRT conferred a higher risk of RRT dependence

Wang et al *NDT* 2018

But let’s ask a more fundamental question

- What is the evidence for a dose of 20-25 mL/kg/hr as he standard of care?

Can we go lower?

LoW Dose-Intensity vs. Standard Dose-Intensity COntinuous Renal ReplaceMent Therapy in Critically Ill Patients (WISDOM): A Pilot Randomized Trial

ClinicalTrials.gov Identifier: NCT06446739

Alberta Health Services

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What are the overarching questions of the WISDOM research program?

- Among critically ill patients with AKI receiving CRRT, is lower dose-intensity, compared with standard dose-intensity
    1. Non-inferior with respect to RRT duration and kidney recovery?
    2. Superior with respect to reducing RRT duration and improving kidney recovery.
- Our ongoing multicentre pilot trial is evaluating the feasibility and tolerability of lower versus standard CRRT dose-intensity

WISDOM, ClinicalTrials.gov Identifier: NCT06446739

WISDOM Pilot Trial: Design

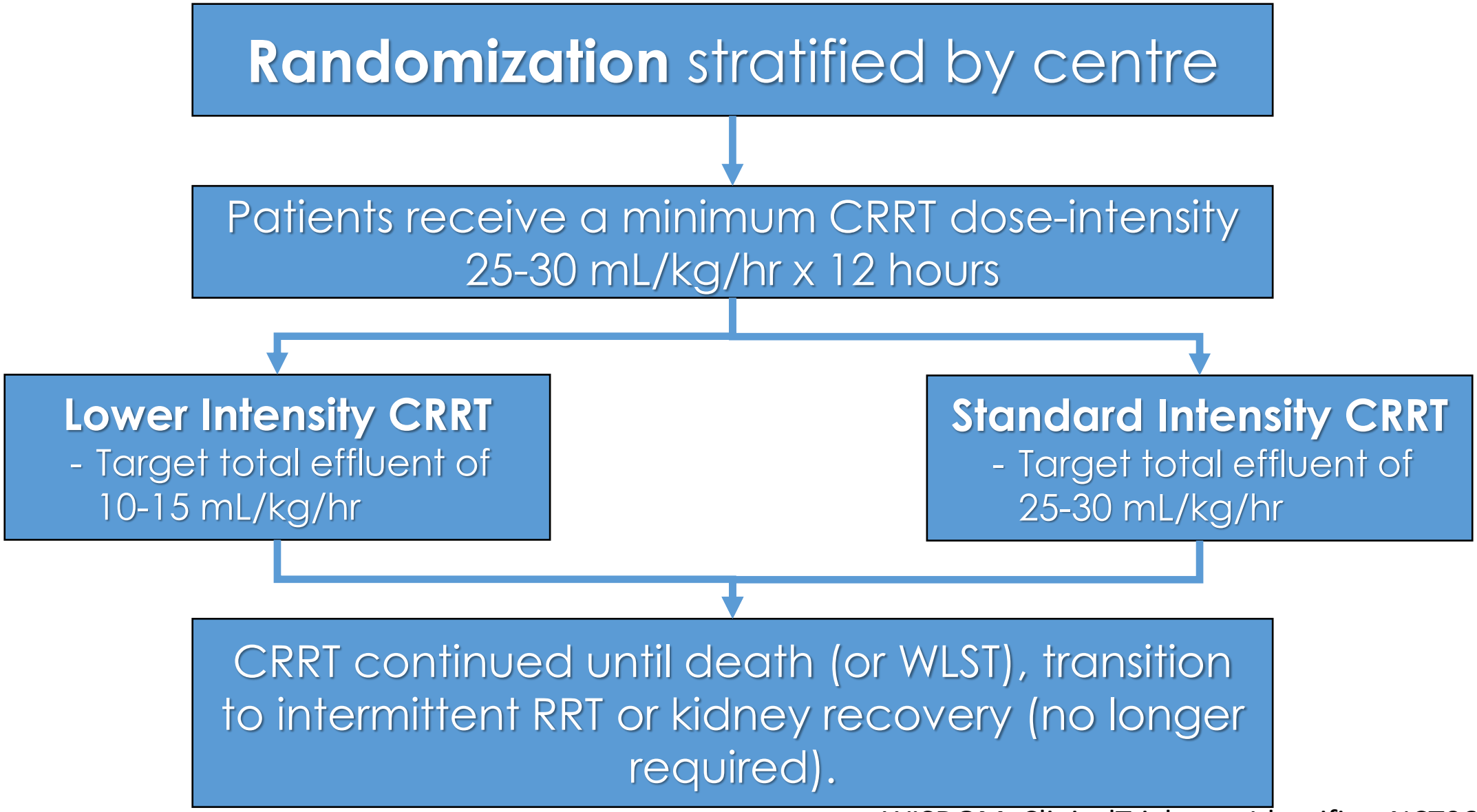
- **Design:** Randomized, open-label, parallel-group, clinical trial of low CRRT dose-intensity vs. standard CRRT dose-intensity

- **Setting:** 5-10 hospitals in Canada, US and UK

- **Target Sample:** 100 patients

WISDOM, ClinicalTrials.gov Identifier: NCT06446739

Eligibility: Adults on CRRT < 24 hrs, anticipated to remain on CRRT for > 48 hours



WISDOM, ClinicalTrials.gov Identifier: NCT06446739

Primary endpoint of the WISDOM pilot trial

- The primary outcome will be the **difference in delivered dose-intensity** between the standard and lower dose-intensity groups. The pilot trial will **target the ability to achieve a minimum difference of 10 mL/kg/hr** in delivered dose-intensity.

- This will be an important proof-of-concept endpoint for scaling to a larger multi-centre trial.

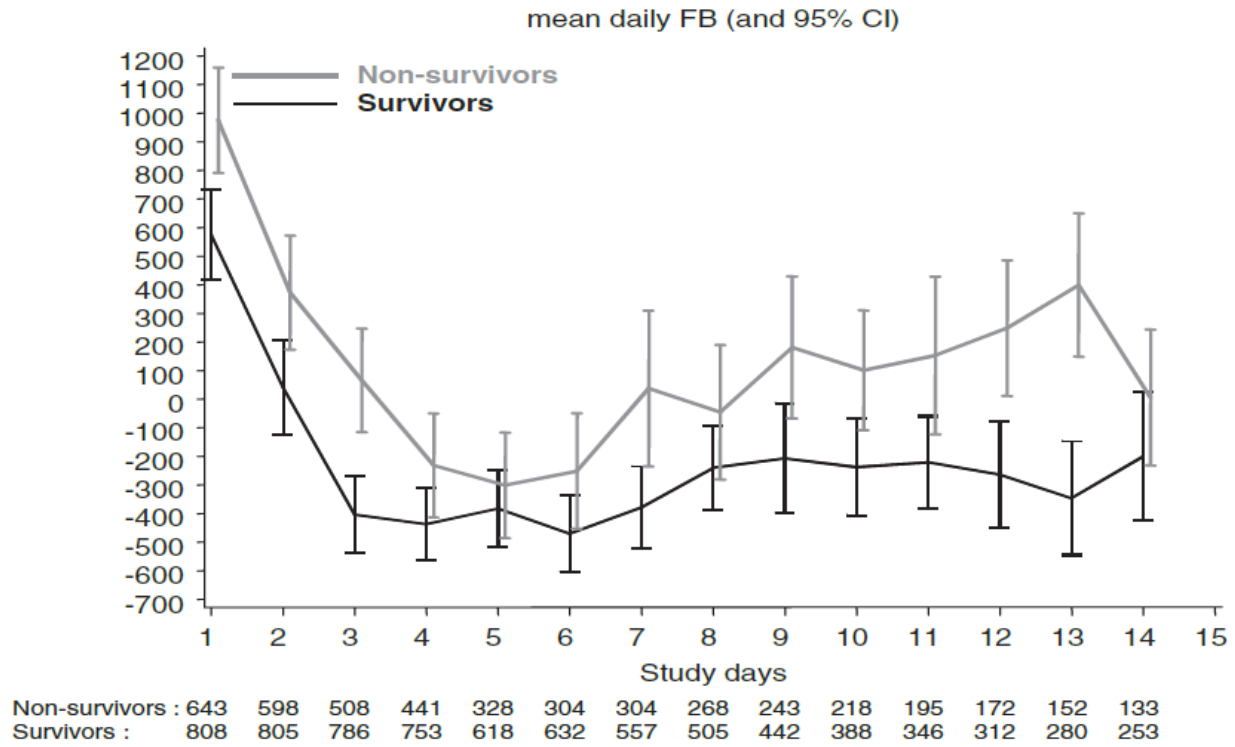
WISDOM, ClinicalTrials.gov Identifier: NCT06446739

The RRT Fluid prescription

- The 2012 Guidelines provide no specific direction regarding optimal fluid target goals when delivering RRT for AKI

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

Achievement of a negative fluid balance associates with better outcomes



RENAL Replacement Study Investigators *Crit Care Med* 2012

Do these data support aggressive ultrafiltration in patients with AKI?

- A less positive fluid balance may be a marker for a healthier patient
  - Sicker patients are more likely to receive more fluid
  - Non-oliguric patient with AKI often closer to recovery than someone oliguric

- Ultrafiltration has risks
  - Iatrogenic hypotension → decreased organ perfusion

Proactive prescription-based fluid management vs usual care in critically ill patients on Kidney Replacement Therapy

Probe-Fluid

Fluid management strategies in AKI

ClinicalTrials.Gov NCT05473143

CRCHUM
CENTRE DE RECHERCHE
Centre hospitalier
de l'Université de Montréal

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

Probe-Fluid
Fluid management strategies in AKI

The question

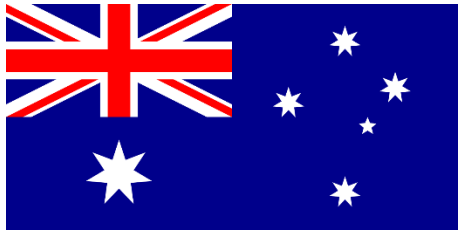
- In critically ill patients with severe AKI receiving RRT, is it possible to perform a pragmatic trial comparing a **proactive fluid management strategy aimed at minimizing fluid accumulation** to usual care and obtain a significant separation in fluid balance between arms ?

Probe-Fluid

Fluid management strategies in AKI

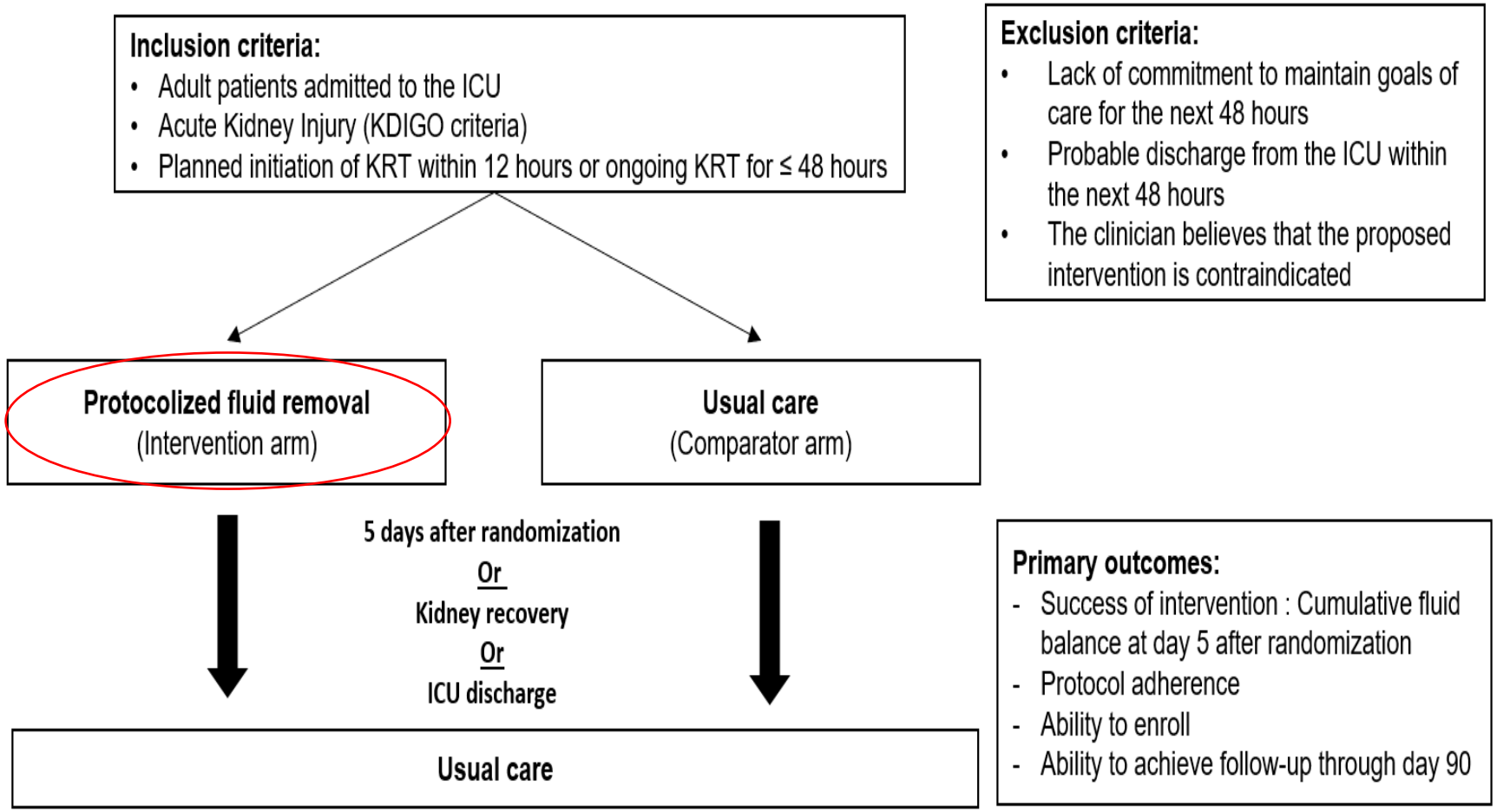
Study design

- Study design: Pilot open-label multinational randomized controlled trial
- Study sites: 15 sites
- Target sample size: 150 participants
- RECRUITMENT COMPLETE



Study flowchart

Probe-Fluid
Fluid management strategies in AKI



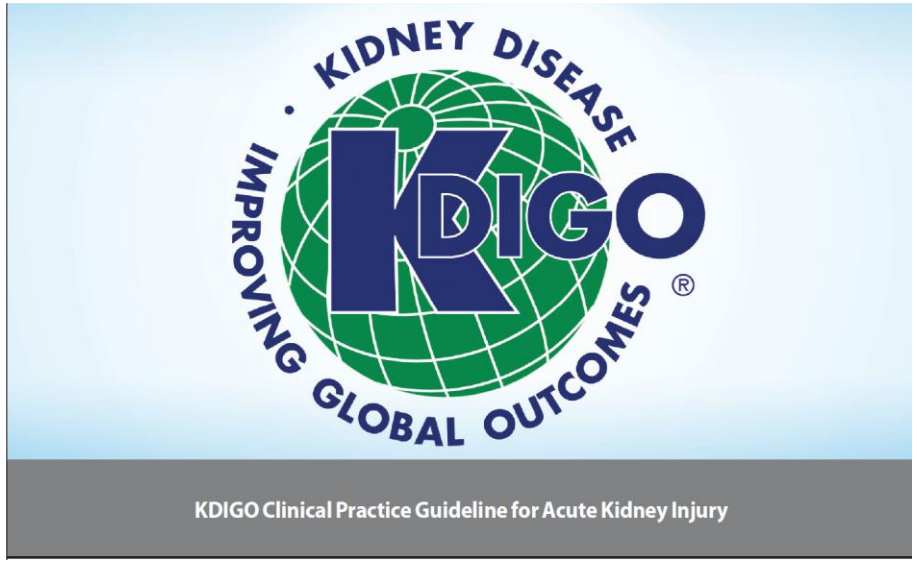
Probe-Fluid, ClinicalTrials.Gov NCT05473143

Probe-Fluid
Fluid management strategies in AKI

The intervention: Protocolized fluid removal

- Clinician must declare fluid balance target each day
- Goal is 2-3% reduction in body weight per day (ie, achieve a net negative fluid balance)
- Minimization of all fluid input (fluid stewardship)
  - Avoid “maintenance” IV infusion
  - Concentrate all IV solutions

When to stop RRT?



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*)

Kidney Int 2012

JAMA | Original Investigation

A Conservative Dialysis Strategy and Kidney Function Recovery in Dialysis-Requiring Acute Kidney Injury

The Liberation From Acute Dialysis (LIBERATE-D) Randomized Clinical Trial

Kathleen D. Liu, MD, PhD, MAS; Edward D. Siew, MD, MSCI; Delphine S. Tuot, MDCM, MAS; Anitha Vijayan, MD; Gonzalo Matzumura Umemoto, MD; Bethany C. Birkelo, DO, MSCI; Benjamin J. Lee, MD, MAS; Y. Diana Kwong, MD, MAS; Ian E. McCoy, MD, MS; Kevin Delucchi, PhD; Hanjing Zhuo, MPH; Chi-yuan Hsu, MD, MSc

Setting:

Four-site study in the US

January 2020-March 2025

221 participants

Liu et al *JAMA* 2025

LIBERATE-D Eligibility

- Inclusion criteria:
  - ≥ 18 years of age
  - Severe AKI-D due to ATN
  - Not requiring vasopressor support
  - Plan for intermittent dialysis
  - Baseline eGFR ≥ 15 mL/min/1.73 m^2
- Exclusion criteria:
  - Non-traditional indication for dialysis
  - Complete nephrectomy as cause of AKI-D
  - Kidney transplant during index hospitalization
  - Dialysis > 3 months
  - Decompensated heart failure requiring left ventricular assist device or continuous inotropic support
  - Mechanical ventilation via endotracheal tube
  - Hypoxemia requiring significant oxygen support

Liu et al *JAMA* 2025

LIBERATE-D: Interventions

Stratification by site and eGFR ≤/> 45 mL/min/1.73 m^2

Conservative strategy: "Aim to defer"

Dialysis only of ≥ 1 of the following:

BUN > 112 mg/dL

Hyperkalemia

Severe metabolic acidosis

Pulmonary edema

Clinician judgement

Conventional Strategy: "Plan to dialyze"

HD three times per week unless:

CrCl > 20 mL/min

Urine output > 1 L/d (>2 L/day with diuretics)

Inter-dialytic decline in serum creatinine

Liu et al *JAMA* 2025

LIBERATE-D: Baseline characteristics

Category	Conservative Dialysis (n=110)	Conventional Dialysis (n=110)
Age, median (IQR), y	55 (43–67)	59 (48–73)
Male, %	64%	71%
White, %	53%	68%
Medical service at admission, %	65%	65%
ICU at randomization, %	40%	39%
Vasopressors before randomization, %	74%	77%
Charlson CI	3 (1–5)	4 (2–6)
Heart failure history, %	27%	22%
Diabetes, %	40%	33%
Cause of AKI – Ischemia, %	65%	70%
Cause of AKI – Nephrotoxin, %	56%	50%
Cause of AKI – Sepsis, %	48%	50%
Baseline eGFR, mean	65.0	64.5
Urine output day prior	238	260

Liu et al *JAMA* 2025

LIBERATE-D: Outcomes

Outcome	Conservative Dialysis (n=109)	Conventional Dialysis (n=109)	Difference (95% CI)	P value
Kidney recovery at discharge, %	70 (64.2)	55 (50.5)	13.8 (0.8–26.8)	0.04
Dialysis / wk, median	1.8 (0–2.6)	3.1 (2.6–3.5)	–1.4 (–1.8 to –1.0)	<.001
Dialysis-free days to day 28	21 (0–28)	5 (0–21)	16 (5–27)	<.001
LOS after randomization, d	14 (8–26)	15.5 (10–28)	–1.5 (–5.8 to 2.8)	.43
In-hospital death, %	10/110 (9.1)	7/109 (6.4)	2.7 (–4.4 to 9.7)	.46
Kidney recovery at day 28, %	71/109 (65.1)	59/109 (54.1)	11.0 (–1.9 to 24.0)	.10
Death by day 28, %	14/110 (12.7)	7/109 (6.4)	6.3 (–1.4 to 14.0)	.11
Kidney recovery at day 90, %	72/108 (66.7)	63/108 (58.3)	8.3 (–4.5 to 21.2)	.21
Death by day 90, %	16/109 (14.7)	20/108 (18.5)	–3.8 (–13.7 to 6.0)	.45

Liu et al *JAMA* 2025

Take home messages

- Acute RRT practice is hampered by limited evidence
- Since the last KDIGO guidelines in 2012, several RCTs have bolstered the quality of evidence but many gaps remain
- Ongoing research programs will shed further light on optimal CRRT dose and fluid prescription
- The recently-completed LIBERATE-D trial has demonstrated the effectiveness of applying a safe and successful RRT weaning strategy

Toronto, Canada

感謝您的關注

我樂意回答任何問題

Tel Aviv, Israel

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