Section	
Title:	**LoW Dose-Intensity vs. Standard Dose-Intensity COntinuous Renal ReplaceMent Therapy in Critically Ill Patients (WISDOM): A Pilot Randomized Trial**
Ethics:	University of Alberta Health Research Ethics File: Pro00140224 – Approved – April 22, 2024.
Background:	An estimated 10-15% of critically ill patients receive RRT, the majority of whom initially receive continuous renal replacement therapy (CRRT). The 2012 *Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines (CPG) for* AKI recommend delivering a CRRT dose-intensity of 20-25 mL/kg/hr. This recommendation is derived from prior RCTs evaluating higher dose-intensity (35-40 mL/kg/hr vs. 20-25 mL/kg/hr) that have not shown any survival advantage. These findings translated to a dose-intensity of 20-25 mL/kg/hr becoming the *de facto* dose-intensity standard for patients receiving CRRT. In addition, because epidemiologic studies describe CRRT dose-intensity practices have consistently found that the "delivered" dose-intensity was often less than "prescribed" (only ~75-90%), usually due to therapy interruptions (i.e., circuit clotting; diagnostic imaging; minor surgical procedures), the 2012 KDIGO CPGs suggest that dose-intensity augmentation is required and that "*a higher prescription"* in the range of 25-30 mL/kg/hr is needed. To date, no RCT has focused on evaluating or defining a minimally acceptable and safe CRRT dose-intensity threshold. Specifically, it is not clear whether a lower dose-intensity (10-15 mL/kg/hr) may be equally acceptable or even superior to the current guideline-directed standard (25-30 mL/kg/hr).
Objective:	The WISDOM research program aims to address whether a lower CRRT dose-intensity (10-15 mL/kg/hr) in critically ill patients with AKI is non-inferior for 90-day mortality compared to the current guideline-directed standard CRRT dose-intensity (25-30 mL/kg/hr) and will secondarily determine if lower CRRT dose-intensity can shorten RRT duration and improve kidney recovery versus the guideline-directed standard.
Study Design:	The LoW Dose-Intensity vs. Standard Dose-Intensity COntinuous Renal ReplaceMent Therapy in Critically Ill Patients (WISDOM) trial is a multi-centre prospective, randomized, open-label, blinded endpoint (PROBE) pilot trial in adult ICU patients with AKI receiving CRRT.
Population:	ICU patients with AKI in whom the clinical team has decided to start CRRT or who are within 24 hours of having started CRRT will be potentially eligible. Each patient will fulfill all inclusion and no exclusion criteria.
Eligibility:	***Inclusion criteria:*** i) age ≥ 18 years ii) patient weight ≥ 55 kg iii) plan to initiate CRRT or within 24 hours of having started CRRT for acute kidney injury (AKI), defined by fulfillment of the KDIGO consensus definition[5] iv) expected to survive and receive CRRT for a duration of ≥ 48 hours v) able to consent or have an authorized representative consent after being informed on the details and risks of participation, unless a waiver or deferred consent process is approved by local REB. ***Exclusion criteria:*** i) indication for sustained higher dose-intensity CRRT (e.g., hyperammonemia in acute liver failure; hyperuricemia in tumor lysis syndrome; hyperkalemia in rhabdomyolysis) ii) end-stage kidney disease receiving maintenance dialysis iii) receipt of intermittent RRT for AKI during the current hospitalization iv) inability to comply with the requirements of the study protocol.
Intervention:	The *experimental arm* will be lower CRRT dose-intensity, defined as a delivered effluent flow rate of **10-15 mL/kg/hr**. The rationale for this lower dose-intensity is based on the observed lower threshold of dose-intensity currently delivered in clinical practice and observational data showing this threshold is acceptable, tolerated and safe. The *control arm* will be guideline-directed standard CRRT dose-intensity, defined as delivered effluent flow rate of **25-30 mL/kg/hr**. The standard dose-intensity is aligned with current practice and by recommendations from international CPGs.[5] The current standard of care for CRRT dose-intensity provided in ICUs in Alberta and across the sites that participated in STARRT-AKI (39 Canadian sites) ranged between 26-30 mL/kg/hr. The CRRT dose calculation will use measured or estimated actual body weight, as previously described and recommended by CPGs. All enrolled patients will receive an active run-in period of standard dose-intensity of up to 24 hours to ensure initial metabolic and azotemic stabilization.
Outcomes:	

Primary Endpoint	The primary feasibility endpoint is the difference (95% CI) in the total delivered effluent flow rate per patient between those in the lower and standard CRRT dose-intensity groups. The WISDOM pilot trial will target the detection of a minimum difference of 10 mL/kg/hr in average delivered dose-intensity between the groups.
Secondary Endpoints	The secondary feasibility endpoints are: i) enrollment rate, with a target average of ≥2 patients/site/month. ii) proportion of eligible patients consented, with a target of >50% of fully eligible patients. iii) time to randomization, with a target of >75% of eligible patients within 12-hours. iv) protocol adherence for allocated CRRT dose-intensity, with a target time in-range of >80%. v) ability to capture delivered CRRT dose-intensity process measures. This is a measure of trial implementation and fidelity, with a target of capture of >95% of daily CRRT dose-intensity (hourly). vi) ability to capture clinical endpoints at 90-days, with a target of >95%.
Biochemical Endpoints	The secondary biochemical endpoints to assess the tolerability of the intervention are: i) daily serum sodium, bicarbonate, base excess, strong ion difference (SID) and pH while receiving CRRT, and number (%) days without severe acidemia (pH <7.25) (excluding day of randomization). ii) daily serum magnesium, potassium, and phosphate while receiving CRRT, and number (%) of days without hyperkalemia (K+ >5.5 mmol/L) (excluding day of randomization). iii) daily serum urea while receiving CRRT, and number (%) of days without serum urea >35 mmol/L (excluding day of randomization).
Process of Care Endpoints	The process of care measures to assess the tolerability of the intervention are: i) daily lowest/highest CRRT dose-intensity delivered for any given hour following randomization. ii) proportion of hours/day when CRRT dose-intensity is in target range. This is a primary protocol adherence process measure and will provide evidence of between group differences in dose-intensity. iii) total treatment time/day while receiving CRRT following randomization. This will be defined as time on treatment divided by 24-hours. iv) total number of hemofilter/circuit replacements during CRRT following randomization. v) total volume of replacement/dialysate fluid used per day following randomization. vi) total number and cumulative doses of supplemental electrolytes (Mg+, K+, PO4-, HCO3-), protein and vitamins administered while receiving CRRT. vii) measure of daily nursing bedside workload, while receiving CRRT following randomization.
Safety	The safety endpoints are: i) occurrence of trial-related adverse and serious adverse events. ii) occurrence of trial-related adverse events and serious adverse events leading to discontinuation of the trial intervention.
Tertiary Outcomes	The WISDOM pilot trial has not been designed to detect differences in patient-centred, kidney-centred or health service-specific outcomes[36], however, we will measure the following tertiary outcomes: duration of RRT; transition from CRRT to IHD; receipt of RRT at hospital discharge, 30-days and 90-days; RRT-free days at 90-days; ICU mortality; hospital mortality; 90-day mortality; a composite of major adverse kidney events (MAKE) at 30-days and 90-days; delta estimated glomerular filtration rate (baseline to 90-days); daily receipt of non-renal organ support (e.g., invasive and non-invasive mechanical ventilation; vasoactive therapy), ICU length of stay, hospital length of stay and re-hospitalization within 90-days.
Sample Size Estimation:	The sample size for the WISDOM pilot trial will address the detection of a minimum difference in the delivered dose-intensity of CRRT between the groups. Based on the ability to detect a minimum difference of 10 mL/kg/hr in dose-intensity, assuming the delivery of 25 mL/kg/hr in the standard dose-intensity group and 15 mL/kg/hr in the lower dose-intensity group, with a conservative standard deviation (SD) of 15, 90% power, and an alpha of 0.05, a total sample of 96 patients is needed (48 patients per group). This will be inflated to 100 patients to account for any withdrawal or dropout.
Registration:	NCT06446739 – June 6, 2024.
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