STARRT AKI

STandard versus Accelerated initiation of Renal Replacement Therapy in Acute Kidney Injury (STARRT-AKI): A Multi-Centre, Randomized, Controlled Trial

ClinicalTrials.gov Identifier: NCT02568722

Objectives: To determine whether, in critically ill patients with severe AKI, a strategy of accelerated (or early/pre-emptive) initiation of RRT, compared to a conservative strategy contributes to:

1. *Improved survival* (primary outcome) at 90 days; and
2. *Recovery of kidney function* (secondary outcome), defined as independence from RRT at 90 days.

Design: Multicentre, open-label, randomized controlled trial will compare an accelerated (or early/pre-emptive) approach to the initiation of RRT versus a conservative strategy of initiation of RRT as guided by standard indications and clinical judgment in critically ill patients with AKI.

Study Population: Two thousand eight hundred sixty six (2,866) critically ill patients with evidence of severe AKI, who do not have an urgent indication for RRT initiation at the time of screening but who have a reasonable likelihood of ultimately requiring RRT. Recruitment will occur at centers in Canada, the USA, Australia, New Zealand, the UK, Austria, Finland, Belgium and potentially several other countries.

***Inclusion Criteria* (all need to be fulfilled):** **1)** Age ≥ 18 years; **2)** Admission to an intensive care unit (ICU); **3)** Evidence of kidney dysfunction [serum creatinine ≥100 μmol/L (women) and ≥ 130 μmol/L (men)] and; **4)** Evidence of severe AKI defined by at least 1 of the following 3 criteria:

i) ≥ 2-fold increase in serum creatinine from known pre-morbid baseline or during the current hospitalization; OR
ii) Achievement of a serum creatinine ≥ 354 μmol/L with evidence of a minimum increase of 27 μmol/L from pre-morbid baseline or during the current hospitalization; OR
iii) Urine output < 6.0 mL/kg over the preceding 12 hours

***Exclusion criteria* (any of the following factors will result in ineligibility):** **1)** Serum potassium >5.5 mmol/L; **2)** Serum bicarbonate <15 mmol/L; **3)** Presence of a drug overdose that necessitates initiation of RRT; **4)** Lack of commitment to ongoing life support (including RRT); **5)** Any RRT within the previous 2 months (either acute or chronic RRT); **6)** Kidney transplant within the past 365 days; **7)** Known pre-hospitalization advanced chronic kidney disease, defined by an estimated glomerular filtration rate <20 mL/min/1.73m^2; **8)** Presence or clinical suspicion of renal obstruction, rapidly progressive glomerulonephritis, vasculitis, thrombotic microangiopathy or acute interstitial nephritis; **9)** Clinician(s) caring for patient believe(s) that immediate RRT is absolutely mandated; **10)** Clinician(s) caring for patient believe(s) that deferral of RRT initiation is mandated.

Accelerated RRT initiation (experimental arm): A dialysis catheter will be placed and RRT initiated as soon as possible and no more than 12 hours after the patient became fully eligible.

Standard RRT initiation (control arm): In the absence of kidney function recovery, the initiation of RRT will be permitted if one of the following develops: **1)** serum potassium ≥6.0 mmol/L; **2)** pH ≤7.20 or serum bicarbonate ≤12 mmol/L; **3)** severe respiratory failure, based on a PaO2/FiO2 ≤200 and clinical perception of volume overload; **4)** and/or persistent AKI >72 hours following the time of randomization. Once a decision is made to start RRT, a dialysis catheter will be placed and RRT initiated as soon as possible. *All other aspects of RRT (i.e. RRT modality, mode, dose, anticoagulation) administered to patients in both arms will follow current best practice and local standards of care.*

Primary outcome: All-cause mortality at 90 days.

Secondary outcomes: **1)** RRT dependence at 90 days; **2)** Composite of death or RRT dependence at 90 days; **3)** Estimated glomerular filtration rate at 90 days; **4)** albuminuria at 90 days; **5)** Major adverse kidney outcomes, defined as death, RRT dependence or eGFR < 75% baseline eGFR) at 90 days; **6)** Ventilator-free days through day 28; **7)** Vasoactive therapy-free days through day 28; **8)** ICU-free days through day 28; **9)** Hospitalization-free days through day 90; **10)** Death in ICU, at 28 days, and in-hospital; **11)** Health-related quality of life (EuroQoL EQ-5D-5L) at day 90 and at 1 year; **12)** Health care costs through 1 year; **13)** Vital status and RRT dependence at 1-year.

Significance: The optimal timing of RRT initiation is an existing knowledge gap and a clear priority for investigation. With the successful completion of the STARRT-AKI pilot trial, the feasibility and relevance of the proposed interventions has been established. It is now time to definitively evaluate whether earlier/pre-emptive/accelerated RRT initiation is associated with enhanced survival as compared to a conservative strategy for initiation of RRT, which is driven by conventional indications and clinician judgment. The findings of the STARRT-AKI are certain to inform the practice and policy around RRT initiation among critically ill patients with severe AKI.

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