Data Creation Plan for Secondary Analyses

Name and Number of Study	**Factors associated with adverse events for patients enrolled in the STARRT-AKI trial**
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DCP Update History	July 27, 2022 (Version 1) Aug 29, 2022 (Version 2) Nov 28, 2023 (Version 3) June 27, 2024 (Version 4)
Short Description of Research Question	What factors are associated with adverse haemodynamic events in patients receiving renal replacement therapy (RRT) in the STARRT AKI trial? Are these haemodynamic events associated with less favorable clinical outcomes?
List of Datasets Used	STARRT-AKI Trial main database
Time of Data Extraction	December 15, 2023.

Defining the Cohort	
Cohort	The subgroup of patients who suffered adverse haemodynamic events in both study arms of STARRT-AKI inclusive of patients who received RRT only.
Exclusion Criteria	Nil
Size of Cohort	Full randomized cohort; including patients experiencing AE (haemodynamic). Confined to patients who received RRT in both arms of the trial.

Time Frame Definitions	
Accrual Start/End Dates	No additional data collection required.
Max Follow-up Date	N/A

Variable Definitions	
Main Exposure or Risk Factor	Receipt of RRT in full randomized cohort of the STARRT-AKI trial.
Baseline Characteristics (Table 1 data)	Age, sex, weight, baseline serum creatinine, baseline eGFR, pre-existing conditions, admission category, cardiopulmonary bypass, aortic aneurysm repair, other vascular surgery, major trauma, obstetric complication, sepsis, septic shock, SAPS II score, SOFA score, mechanical ventilation, vasoactive support, serum potassium, serum bicarbonate, median urine output, median cumulative fluid balance, heart rate, systolic blood pressure, temperature, fluid balance, CFS score. Factors at randomization and at RRT initiation will be considered.
Covariates **(To Inform Model Development)**	Age, sex, weight, CKD, hypertension, diabetes mellitus, heart failure, coronary artery disease, liver disease, sepsis, septic shock, SAPS II score, SOFA score, mechanical ventilation, vasoactive support, serum potassium, serum bicarbonate, median cumulative fluid balance, RRT modality, IHD parameters, CRRT parameters, anticoagulation, ultrafiltration rate. Factors at randomization and at RRT initiation will be considered. Allocated RRT initiation strategy will be evaluated as a covariate/interaction term.
Outcome(s) Definitions	Haemodynamic adverse event, defined as either a hypotensive episode or arrhythmic adverse event after RRT initiation during the STARRT AKI trial.

Outline of Analysis Plan	
Primary Outcome Variables	Factors associated with occurrence of a haemodynamic adverse event (hypotension and/or arrhythmia) after RRT initiation during the study period.
Secondary Outcome Variables	Dialysis dependence at 90 days, as well as at ICU discharge, hospital discharge and at 28 days, according to whether or not haemodynamic adverse events occurred (multivariable analysis). Mortality in ICU, in hospital, at 28 days and at 90-days according to whether or not a haemodynamic adverse event occurred. ICU and hospital lengths of stay; ventilator and vasoactive-free days at 28 days. RRT-free days at 90-days. Analysis of the interaction between RRT initiation strategy and a haemodynamic adverse event will be explored. If there is evidence of significant interaction, further subgroup analysis by allocated RRT initiation strategy (e.g., accelerated vs. standard) will be performed. Sensitivity analyses: 1) occurrence of early (<3 days), intermediate (3-6) or late (7-14 days) occurrence of haemodynamic adverse events according to RRT initiation strategy (event explored in histogram to optimized discrete

	periods); 2) description of characteristics, treatments and outcomes of patients have >1 haemodynamic adverse event. Subgroup analysis: 1) baseline cardiovascular comorbidity (e.g., hypertension; heart failure); 2) baseline liver disease; 3) illness acuity (e.g., SAPS II score; SOFA score); 4) surgical status; 5) sepsis; 6) receiving vasoactive therapy; 7) receiving invasive mechanical ventilation; 8) fluid balance at RRT initiation; and 9) ultrafiltration rate.
Detailed Analysis Plan	Continuous variables will be examined graphically and recorded as means (+/- standard deviation) for normally distributed data or medians (with IQRs) for non-normally distributed data. Comparisons will be made using T tests or Wilcoxon rank sum tests as appropriate. Categorical variables will be examined by frequency distribution and recorded as proportions. The primary analysis will be a cause-specific Cox proportional hazards regression model using the Fine & Gray method as a sensitivity analysis to derive sub distribution hazard ratios for the risk of a haemodynamic adverse event during the study period according to patient characteristics and RRT treatment allocation with a competing risk (censored) for death. We will conduct univariate analysis that will assess the effect of the individual covariate on the risk of haemodynamic adverse event. Multivariable models will be conducted to derived adjusted estimates: one multivariable model will estimate adjusted associations between baseline characteristics and haemodynamic adverse event, and a second model will estimate adjusted associations between RRT initiation variables and haemodynamic adverse event. The second model will be adjusted by baseline variables as potential confounders. To derive a model for risk of haemodynamic adverse events, the dataset will be randomly split, with 60% of participants allocated to derivation and 40% to validation sets. Within the derivation subset, we will utilize a multivariable Cox proportional hazards model based on the least absolute shrinkage and selection operator (LASSO), which will include time to haemodynamic adverse event as the dependent variable and, initially, demographics, clinical and laboratory baseline and RRT initiation covariates as predictors. Tenfold cross-validation will be used to select the optimal lambda value that minimizes mean squared prediction error. This model will identify the set of variables that best predict the risk of haemodynamic adverse events. A two-tailed p value < 0.05 will be considered evidence of statistical significance for all estimates. Plan for a 2-stage analysis: 1. Assessment of factors associated with occurrence of a haemodynamic adverse event (hypotension and/or arrhythmia) during the study period. 2. Assessment of the effect of haemodynamic adverse events during RRT on patients outcomes (dialysis dependence/mortality/LOS/RRT-free days/ventilator-free days/vasoactive-free days).
Proposed Tables and Figures	Table 1: Baseline characteristics of the subgroup in each study arm who received RRT and experienced a haemodynamic adverse event during STARRT-AKI. Table 2: Treatment characteristics of the subgroup in each study arm who

	received RRT and experienced a haemodynamic adverse event during STARRT-AKI. Table 3: Univariate analysis of factors associated with occurrence of a haemodynamic adverse event during STARRT-AKI. Table 4: Multivariate model of factors associated with occurrence of a haemodynamic adverse event. Figure 1: Timing of occurrence of a haemodynamic adverse event in relation to initiation of RRT during STARRT-AKI (Kaplan-Meier curve stratified by study arm [note – time 0 will be start of RRT initiation – not randomization]).

Mock-up tables

Table 1: Baseline characteristics at RRT initiation of patients who or did not experience a haemodynamic adverse event during STARRT-AKI[*]

Characteristic	**Haemodynamic adverse event experienced (N =)**	**No haemodynamic adverse event experienced (N =)**	**P-value**
Age, years, mean (SD)			
Female sex, n/total (%)			
Weight, kg, mean (SD)			
Serum creatinine, mg/dl, mean (SD)			
Estimated glomerular filtration rate, ml/min/1,73 m^2, mean (SD)			
Pre-existing conditions, n/total (%)			
Chronic kidney disease			
Hypertension			
Diabetes mellitus			
Heart failure			
Coronary artery disease			
Liver disease			
Metastatic cancer			
Hematologic cancer			
HIV infection or AIDS			
Admission category, n/total (%)			
Scheduled surgery			
Unscheduled surgery			
Medical			
Hospital-acquired risk factor for AKI in previous week, n/total (%)			
Cardiopulmonary bypass			
Aortic aneurysm repair			
Other vascular surgery			
Major trauma			

Obstetric complication			
Clinical condition at randomization			
Sepsis, n/total (%)			
Septic shock, n/total (%)			
SAPS II value, mean (SD)			
SOFA score, mean (SD)			
Mechanical ventilation, n/total (%)			
Vasoactive support, n/total (%)			
Serum potassium, mmol/L, mean (SD)			
Serum bicarbonate, mmol/L, mean (SD)			
Median urine output, ml/24 hours, median (IQR)			
Median cumulative fluid balance, ml, median (IQR)			
Heart rate, bpm, mean (SD)			
Systolic blood pressure, mm Hg, mean (SD)			
Temperature, degrees Celsius, mean (SD)			
Clinical Frailty Scale score, mean (SD)			

[*]Cohort confined to patients who received RRT in both arms of the STARRT-AKI trial.

Table 2: Treatment characteristics of the initial RRT prescription for patients who or did not experience a haemodynamic adverse event during STARRT-AKI[*]

Characteristic	Haemodynamic adverse event experienced (N =)	No haemodynamic adverse event experienced (N =)	P-value
RRT modality, n/total (%)			
CRRT			
IHD			
SLED			
Dialysis catheter insertion site, n/total (%)			
Jugular			
Femoral			
Subclavian			
Intermittent RRT duration prescribed, hours, median (IQR)			
IHD			
SLED			
CRRT dose prescribed, ml/kg/hour, median (IQR)			
Anticoagulation, n/total (%)			
Citrate			
Heparin			
None			
Other			
Ultrafiltration achieved during 1st RRT session, ml, median (IQR)			

[*]**Cohort confined to patients who received RRT in both arms of the STARRT-AKI trial.**

Table 3: Univariate analysis of factors associated with occurrence of a haemodynamic adverse event during STARRT-AKI.

Factor	Univariate HR	Univariate P-value
Age		
Female sex		
Weight		
Chronic kidney disease		
Hypertension		
Diabetes mellitus		
Heart failure		
Coronary artery disease		
Liver disease		
Sepsis		
Septic shock		
SAPS II score		
SOFA score		
Mechanical ventilation		
Vasoactive support		
Serum potassium		
Serum bicarbonate		
Median cumulative fluid balance		
RRT treatment strategy (accelerated vs standard)		
RRT modality		
RRT blood flow rate (if available)		
CRRT dose prescribed		
RRT anticoagulation		
Ultrafiltration achieved during 1st RRT session		

Table 4: Multivariate analysis of factors associated with occurrence of a haemodynamic adverse event during STARRT-AKI.

Factor	Model 1 HR	Model 1 P-value	Model 2 HR	Model 2 P-value
Age				
Female sex				
Weight				
Chronic kidney disease				
Hypertension				
Diabetes mellitus				
Heart failure				
Coronary artery disease				
Liver disease				
Sepsis				
Septic shock				
SAPS II score				
SOFA score				
Mechanical ventilation				
Vasoactive support				
Serum potassium				
Serum bicarbonate				
Median cumulative fluid balance				
RRT treatment strategy (accelerated vs standard)				
RRT modality				
RRT blood flow rate (if available)				
CRRT dose prescribed				
RRT anticoagulation				

type				
Ultrafiltration achieved during 1st RRT session				

Figure 1: Timing of occurrence of a haemodynamic adverse event in relation to initiation of RRT in STARRT AKI (Kaplan Meier curve stratified by study [note – time 0 will be start of RRT initiation – not randomization]).