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Factors associated with adverse haemodynamic events during the STARRT-AKI trial: a post-hoc secondary analysis

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Abstract

Introduction Haemodynamic adverse events related to renal replacement therapy are a complication of all RRT modalities used in the ICU, including intermittent haemodialysis (IHD), sustained low efficiency dialysis (SLED) and continuous renal replacement therapy (CRRT). At present it is unclear which risk factors predispose to HAE and whether these contribute to adverse patient outcomes.

Methods We performed a secondary analysis of the multinational STARRT-AKI trial to assess factors associated with the occurrence of haemodynamic adverse events (HAE) in patients receiving RRT and whether these HAE were associated with less favourable clinical outcomes. The primary analysis was a multivariable Cox proportional hazards model based on the least absolute shrinkage and selection operator (LASSO), which included time to HAE as the dependent variable.

Results Factors significantly associated with an increased hazard ratio (HR) for HAE during RRT were a higher SOFA score at RRT initiation (HR 1.05; 95% CI 1.00–1.10), use of IHD as the initial RRT modality in comparison to CRRT (HR 1.74; 95% CI 1.28–2.37) and use of SLED as the initial RRT modality in comparison to CRRT (HR 2.73; 95% CI 1.65–4.51). In a multivariable analysis, adjusted for baseline patient characteristics and RRT initiation covariates, there was no significant association between the occurrence of a HAE during RRT and mortality, dialysis dependence, length of stay, RRT-free days, ventilator-free days or vasoactive-free days, respectively. There was, however, a significant association between multiple haemodynamic adverse events and all-cause mortality at 90 days.

Conclusions In this secondary analysis of the STARRT-AKI trial, the use of intermittent RRT modalities and higher severity of illness were associated with HAE during RRT. These events were not significantly associated with adverse clinical outcomes, apart from a significant association between multiple HAE and all-cause mortality at 90 days.

Keywords Acute kidney injury, Renal replacement therapy, Haemodynamic adverse events, Hypotension; arrhythmia

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Introduction

Haemodynamic adverse events (HAE) related to renal replacement therapy (RRT) are a common and much-feared complication of all RRT modalities used in the ICU, including intermittent haemodialysis (IHD), sustained low efficiency dialysis (SLED) and continuous renal replacement therapy (CRRT). Mechanisms that contribute to HAE include patient-related factors such as hypovolaemia, systolic/diastolic dysfunction and decreased vascular tone from distributive shock, along with RRT-related factors including excessive ultrafiltration, rapid osmotic/oncotic shifts, myocardial stunning, lower dialysate calcium and potassium concentrations and dialyser bio-incompatibility [1]. HAE has been shown to affect 10–70% of IHD treatments [2–5] and 19–43% of CRRT treatments [6, 7]. HAE is associated with an increased risk of in-hospital mortality and potentially decreased resolution of AKI and kidney recovery [8, 9]. However, there remains limited understanding of the predisposing factors associated with HAE and, at present, there is little high-quality evidence to guide prevention and treatment of HAE [10].

The Standard versus Accelerated Initiation of Renal Replacement Therapy in Acute Kidney Injury (STARRT-AKI) trial was a multinational, randomized, controlled trial in which critically ill patients with severe acute kidney injury (AKI) were randomly assigned to receive an accelerated RRT strategy (in which RRT was initiated within 12 h of meeting eligibility criteria) or a standard RRT strategy (in which RRT was discouraged unless conventional indications developed or AKI persisted for >72 h) [11]. There was no difference in the primary outcome of death from any cause at 90 days but findings from the trial noted an increased incidence of adverse events in the accelerated-strategy group compared to the standard-strategy group (23% vs. 16.5%, $p < 0.001$). Hypotension during RRT was one of the most common adverse events, with a significant between-group difference (8.7% for accelerated-strategy vs. 5.6% for the standard-strategy, $p < 0.001$). The international STARRT-AKI trial therefore offers an opportunity to evaluate factors associated with HAE in a large heterogeneous population of patients who received different RRT initiation strategies.

The aim of this study, therefore, was to perform a secondary analysis of the STARRT-AKI trial to assess which factors are associated with haemodynamic adverse events (HAE), to develop a reliable prediction model for a HAE, and to explore the relationship between a HAE and clinical outcomes.

Methods

Study design

We performed a secondary analysis of the multinational STARRT-AKI trial which was conducted at 168 centres in

15 countries (Data Creation Plan available at: https://www.ualberta.ca/en/critical-care/media-library/documents/dcp_starrt-aki_hemodynamic-adverse-events4_june-27-2024.pdf). Details of the protocol, statistical analysis plan and main findings have been previously published [11–13]. The STARRT-AKI trial was approved by the health research ethics boards at the University of Alberta (File # Pro00060023), Unity Health Toronto (CTO Project ID: 0761) and the institutional review board at each participating site. Depending on local standards and legislation, informed consent was obtained from patients and substitute decision-makers or through waived consent.

Population

Patients from the full randomized trial cohort who received RRT in both arms of the trial were eligible for inclusion in this analysis. HAEs were defined by the trial investigators as the occurrence of RRT-associated hypotension and/or arrhythmia during RRT (<https://www.ualberta.ca/en/critical-care/media-library/documents/research-documents/starrtaki-manual-of-operations-v-4-0--02apr2018--clean.pdf>). RRT-associated hypotension was defined as a drop in blood pressure of any magnitude requiring one of: initiation of a vasopressor during the RRT session or a need to escalate the vasopressor dose during the RRT session or premature discontinuation of the RRT session due to the blood pressure drop, Arrhythmia during RRT was defined as a new atrial (excluding sinus tachycardia or sinus arrhythmia) or ventricular tachycardia that develops during RRT and which was not present prior to initiation of RRT.

Predictors of hemodynamic adverse events

The primary basis for inclusion was receipt of RRT in the full randomized cohort of the STARRT-AKI trial. The potential risk factors for HAE which were assessed included age, sex, weight, pre-existing chronic kidney disease (CKD), hypertension, diabetes mellitus, heart failure, coronary artery disease, liver disease, sepsis, septic shock, Simplified Acute Physiology score II (SAPS II), Sequential Organ Failure Score (SOFA) score, mechanical ventilation, vasoactive support, serum potassium, serum bicarbonate, median cumulative fluid balance, RRT modality, IHD and CRRT parameters including blood flow rate, ultrafiltration rate, CRRT dose, anticoagulation and IHD/SLED duration. Risk factors both at treatment randomization and at RRT initiation were considered, as many important patient characteristics, e.g. age, sex, comorbidities and SAPS II score, do not change between randomisation and RRT initiation. We also included characteristics at RRT initiation which do change in a time-dependent manner, e.g. laboratory values and fluid balance. Of note, initial RRT modality in the STARRT-AKI trial was guided by patient haemodynamic status at

the time of treatment initiation, with CRRT or SLED recommended for patients with a cardiovascular component of the SOFA score ≥ 2 . A subsequent transition of RRT modality from CRRT/SLED to IHD was recommended if patients had remained off continuous vasopressor and/or inotrope infusions for the previous 12 h (i.e. SOFA_{CV} had decreased to < 2). We restricted our analysis to the initial RRT modality received, as the majority of patients in the STARRT-AKI trial did not change RRT modalities during the trial.

Outcomes

The primary outcome was the occurrence of HAE (hypotension and/or arrhythmia) after RRT initiation during the patient's stay in the ICU or up to 14 days following randomization.

Subsequently, we examined the relationship between HAE and the following outcomes: dialysis dependence at 90 days; all-cause mortality at 90 days, ICU and hospital length of stay; and ventilator- and vasoactive-free days at 28 days. We also performed sensitivity analyses to assess occurrence of early (< 3 days), intermediate (3–6 days) or late (7–14 days) HAE according to RRT initiation strategy (events were explored in a histogram to optimize discrete time-periods); and to describe the characteristics, treatments and outcomes of patients with > 1 HAE.

Statistical analysis

Baseline continuous variables were examined graphically and recorded as means (\pm standard deviation) for normally distributed data or medians (with IQRs) for non-normally distributed data. Comparisons were made using parametric (T-tests or Wald test) tests or non-parametric (Wilcoxon rank-sum tests or Kruskal-Wallis test) tests as appropriate. Baseline categorical variables were examined by frequency distribution, and recorded as proportions. Comparisons were made using Fisher's exact test. To assess the risk of a HAE during the study period according to patient characteristics and RRT treatment allocation, we performed a cause-specific Cox proportional hazards regression model analysis, censoring patients that died without a HAE, and used the Fine & Gray method as a sensitivity analysis to derive subdistribution hazard ratios to account for the competing risk of death. We conducted univariate analysis to assess the association of individual covariates and the risk of HAE. Multivariable models were conducted to derive adjusted estimates: one multivariable model estimated adjusted associations between baseline characteristics and HAE, and a second model estimated associations between RRT initiation variables and HAE, adjusted for baseline characteristics as potential confounders. The primary analysis was a model derived to assess the risk of HAE, in which the dataset was randomly split, with 60% of participants

allocated to derivation and 40% to validation sets. Within the derivation subset, we utilized a multivariable Cox proportional hazards model based on the least absolute shrinkage and selection operator (LASSO), which included time to HAE as the dependent variable and, initially, demographics, clinical and laboratory baseline and RRT initiation covariates as predictors. Tenfold cross-validation was used to select the optimal lambda value that minimized mean squared prediction error. This model identified the set of variables that best predicted the risk of HAE. Model calibration was assessed using a calibration plot. Discrimination was assessed by splitting the derivation and validation sets into groups of low and high predicted risk using the median predicted risk score from the derivation set; and using a Kaplan-Meier plot to evaluate the performance of the risk score in predicting HAE. We also calculated the Gönen and Heller's *K* statistic, which is an extension to time-to-event data of the area under the ROC curve – a commonly used statistic to assess the discrimination of logistic regression models [14]. A multivariable logistic or linear regression model was then used to assess the association between single or multiple HAE during RRT and patient outcomes, including dialysis dependence, mortality, length of stay, RRT-free days, ventilator-free days and vasoactive-free days. A two-tailed P-value < 0.05 was considered evidence of statistical significance for all estimates. There was no adjustment in the analyses for multiplicity of testing.

Results

Baseline characteristics at RRT initiation of patients who or did not experience HAE during STARRT-AKI

Among the 2,992 participants who underwent randomisation in STARRT-AKI, 620 patients did not initiate RRT, and 219 patients had missing values for at least one covariate of interest. Therefore, we restricted our cohort of interest to 2153 patients in total. Of these 2153 patients, 233 (10.8) patients experienced at least one HAE during RRT throughout the study period. Most of these adverse events occurred in the first 48 h on RRT, regardless of treatment modality (Fig. 1a and b). As compared to patients who did not experience HAE, these patients were more frequently in the accelerated-strategy arm and more frequently had IHD or SLED as their initial RRT treatment (Table 1). Patients who experienced HAE had significantly higher SAPS II, SOFA and CV-SOFA scores, were more frequently post cardiopulmonary bypass and were more frequently mechanically ventilated and on vasoactive medications at the time of randomization. They also had a significantly higher cumulative fluid balance and a lower systolic blood pressure at randomization; as well as a higher cumulative fluid balance at RRT initiation.

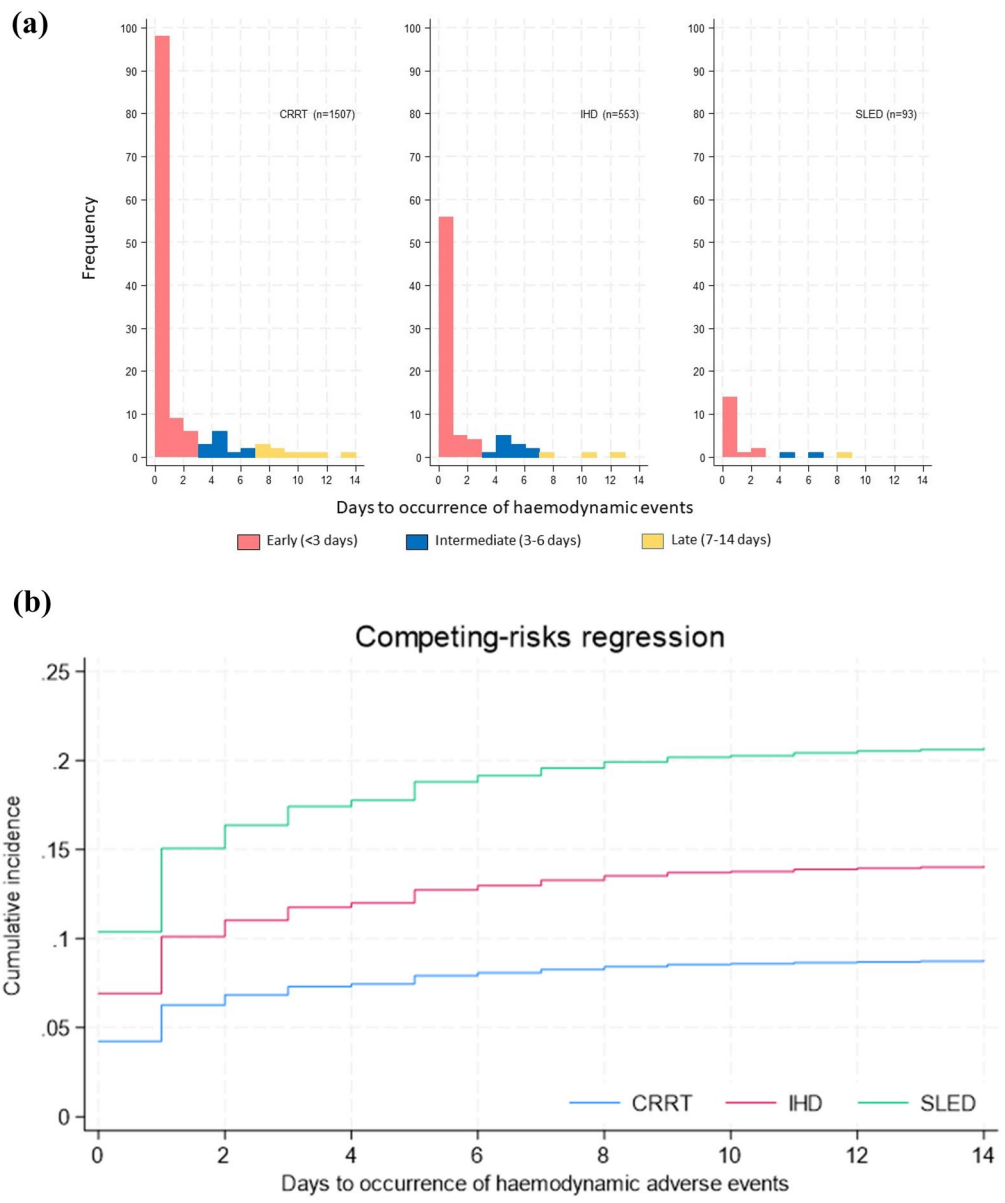


Fig. 1 (a) Histogram of time to occurrence of haemodynamic events (days). (b) Cumulative incidence of HAE over time according to RRT modality (with a competing risk of death)

Factors associated with occurrence of HAE during RRT

In a univariate analysis of potential risk factors for HAE, SAPS II score, mechanical ventilation, SOFA score at RRT initiation, vasoactive medication at RRT initiation, cumulative fluid balance at RRT initiation, IHD or SLED as initial RRT modality, CRRT dose and either IV heparin or no anti-coagulation for RRT were all significantly associated with an increased cause-specific hazard ratio for HAE (Table 2). We also used the Fine & Gray method as a sensitivity analysis to derive subdistribution hazard ratios for the risk of HAE during the study period according to patient characteristics and RRT treatment allocation to account for a competing risk (censored) of death

(Supplemental Table S1). Of note, we found no significant competing risk for death in this sensitivity analysis; with sub-distribution hazard ratios very similar to the univariate cause-specific hazard ratios derived in Table 2.

Multivariable analysis of factors associated with occurrence of HAE during RRT

In a multivariable model of potential risk factors independently associated with HAE, mechanical ventilation, intermittent RRT modalities as the initial RRT modality and CRRT dose were all significantly associated with an increased risk of HAE during RRT (Supplemental Table S2).

Table 1 Baseline characteristics at RRT initiation of patients who or did not experience a haemodynamic adverse event during RRT

| Characteristics | Haemodynamic AE | | P-value |
|--|---------------------|---------------------|---------|
| | Yes (n = 233) | No (n = 2742) | |
| Randomized RRT strategy (%) | | | < 0.001 |
| Accelerated | 143 (61.4) | 1180 (61.5) | |
| Standard | 90 (38.6) | 740 (38.5) | |
| Initial RRT (%) | | | < 0.001 |
| CRRT | 134 (57.5) | 1373 (71.5) | |
| IHD | 79 (33.9) | 474 (24.7) | |
| SLED | 20 (8.6) | 73 (3.8) | |
| Age (Years) | 64.7 (13.5) | 64.3 (14.2) | 0.73 |
| Body weight (Kg) | 89.0 (27.5) | 87.1 (25.7) | 0.29 |
| Female sex (%) | 75 (32.2) | 610 (31.8) | 0.88 |
| Baseline sCr, mg/dl, SD | 1.3 (0.8) | 1.4 (1.1) | 0.28 |
| Baseline GFR, (ml/min/1.73 m ²), SD | 67.2 (28.5) | 66.2 (30.0) | 0.63 |
| Pre-existing conditions | | | |
| Chronic kidney disease (%) | 97 (41.6) | 850 (44.3) | 0.48 |
| Hypertension (%) | 128 (54.9) | 1052 (54.8) | 1.00 |
| Diabetes mellitus (%) | 75 (32.2) | 559 (29.1) | 0.36 |
| Heart failure (%) | 33 (14.2) | 246 (12.8) | 0.54 |
| Coronary artery disease (%) | 44 (18.9) | 420 (21.9) | 0.31 |
| Liver disease (%) | 29 (12.4) | 228 (11.9) | 0.83 |
| Characteristics at randomization | | | |
| SOFA score, SD | 12.8 (3.6) | 12.0 (3.5) | < 0.001 |
| CV-SOFA score, SD | 2.9 (1.6) | 2.6 (1.7) | 0.011 |
| SAPS II Score, SD | 62.6 (15.7) | 59.7 (17.3) | 0.016 |
| sCr at randomization, mg/dl, SD | 3.4 (1.4) | 3.6 (1.7) | 0.14 |
| Cardiopulmonary bypass (%) | 27 (11.6) | 147 (7.7) | 0.042 |
| Aortic aneurysm repair (%) | 16 (6.9) | 92 (4.8) | 0.20 |
| Other vascular surgery (%) | 12 (5.2) | 103 (5.4) | 1.00 |
| Trauma (%) | 11 (4.7) | 75 (3.9) | 0.59 |
| Sepsis in the last 72 h (%) | 149 (63.9) | 1145 (59.6) | 0.23 |
| Mechanical ventilation (%) | 204 (87.6) | 1509 (78.6) | < 0.001 |
| Vasoactive medication (%) | 185 (79.4) | 1371 (71.4) | 0.01 |
| Cumulative fluid balance at randomization, mL, SD | 3510 (1315 to 6659) | 2687 (850 to 5500) | 0.003 |
| Serum potassium, mmol/L, SD | 4.6 (0.8) | 4.5 (0.8) | 0.52 |
| Serum bicarbonate, mmol/L, SD | 19.4 (4.7) | 19.5 (4.4) | 0.68 |
| Urine output, mL, SD | 361 (160 to 800) | 430 (170 to 900) | 0.21 |
| Heart rate, bpm, SD | 109.4 (24.4) | 107.8 (26.8) | 0.39 |
| Systolic blood pressure, mmHg, SD | 96.3 (24.9) | 101.8 (27.7) | 0.004 |
| Temperature, C, SD | 37.4 (1.4) | 37.5 (1.3) | 0.75 |
| Characteristics at RRT initiation | | | |
| Cumulative fluid balance at RRT initiation, mL, median (IQR) | 4410 (1530 to 8876) | 3422 (1098 to 7158) | 0.009 |
| Serum creatinine, mg/dL, SD | 4.0 (1.8) | 4.1 (2.0) | 0.72 |

Table 1 (continued)

| Characteristics | Haemodynamic AE | | P-value |
|-------------------------------|------------------|------------------|---------|
| | Yes (n = 233) | No (n = 2742) | |
| Serum potassium, mmol/L, SD | 4.5 (0.7) | 4.5 (0.7) | 0.16 |
| Serum bicarbonate, mmol/L, SD | 20.1 (4.8) | 20.2 (4.5) | 0.89 |

HR=hazard ratio; RRT=renal replacement therapy; CRRT=continuous renal replacement therapy; CV-SOFA=cardiovascular sequential organ failure assessment; IHD=intermittent hemodialysis; SLED – sustained low efficiency dialysis; IV=intravenous; SOFA=sequential organ failure assessment; SAPS=simplified acute physiology score; sCr=serum creatinine.

Primary analysis

In a multivariable Cox proportional hazards model based on the least absolute shrinkage and selection operator (LASSO), which included time to HAE as the dependent variable, IV heparin or no anti-coagulation for CRRT, IHD or SLED as initial RRT modality, SOFA score at RRT initiation, vasoactive medication at RRT initiation, serum potassium at RRT initiation, fluid balance at RRT initiation, CKD, sepsis and diabetes mellitus were all identified as important predictors of HAE. However, only IHD or SLED as initial RRT modality, no anticoagulation for CRRT and SOFA score at RRT initiation were found to be significantly associated with time to HAE occurrence (Table 3). A calibration plot for observed versus expected results for the LASSO model showed a moderate degree of agreement between predictions and observations using this model (Fig. 2). A Kaplan-Meier curve of patients at high versus low-risk for HAE based on the LASSO model showed good discrimination between patients considered to be at low or high risk, but the *K* statistic was 0.60, indicating only a modest discrimination (Fig. 3). As an additional sensitivity analysis, we compared these results with those achieved by performing a multivariable analysis using the AIC to identify the set of variables that best predicted the risk of HAE (Supplemental Table S3). There was no meaningful difference in the results achieved with the AIC method compared to use of the LASSO method in our multivariable analysis.

Analysis of the association between HAE and patient outcomes

In an unadjusted analysis of the association of HAE on patient outcomes, there was an increased risk of all-cause mortality at 90 days associated with HAE (Table 4). There were also significantly fewer vasoactive-free and ventilator-free days at 28 days associated with HAE. However, in a multivariate analysis, which was adjusted by baseline and RRT initiation covariates, there was no significant association between HAE and patient outcomes.

Table 2 Univariate analysis of factors associated with occurrence of a haemodynamic adverse event during RRT

| | Cause-specific HR (95%) | P-value |
|--|-------------------------|---------|
| Age | 1.00 (0.99–1.01) | 0.60 |
| Female sex | 0.99 (0.75–1.30) | 0.93 |
| Body weight | 1.00 (1.00–1.01.00.01) | 0.31 |
| Chronic kidney disease | 0.90 (0.70–1.17) | 0.44 |
| Hypertension | 1.01 (0.78–1.31) | 0.91 |
| Diabetes Mellitus | 1.15 (0.87–1.51) | 0.33 |
| Heart failure | 1.14 (0.79–1.64) | 0.49 |
| Coronary artery disease | 0.87 (0.63–1.21) | 0.40 |
| Liver disease | 1.06 (0.72–1.56) | 0.77 |
| Sepsis | 1.19 (0.91–1.56) | 0.19 |
| SAPS II score | 1.01 (1.00–1.02.00.02) | 0.007 |
| Randomised to accelerated RRT strategy | 1.03 (0.79–1.33) | 0.85 |
| Mechanical ventilation | 1.88 (1.28–2.78) | 0.001 |
| SOFA score at RRT initiation | 1.08 (1.04–1.12) | <0.001 |
| Vasoactive medication at RRT initiation | 1.63 (1.21–2.18) | 0.001 |
| Serum potassium at RRT initiation | 1.15 (0.96–1.37) | 0.12 |
| Serum bicarbonate at RRT initiation | 0.99 (0.97–1.02) | 0.71 |
| Cumulative fluid balance at RRT initiation | 1.02 (1.00–1.03.00.03) | 0.025 |
| Initial RRT (reference CRRT) | | |
| IHD | 1.62 (1.23–2.14) | <0.001 |
| SLED | 2.53 (1.58–4.04) | <0.001 |
| Ultrafiltration rate (per 100 ml) | 0.99 (0.98–1.00.98.00) | 0.05 |
| Anticoagulation (ref. regional citrate) | | |
| IV heparin | 1.49 (1.09–2.04) | 0.013 |
| None | 1.85 (1.35–2.53) | <0.001 |
| Other | 0.96 (0.35–2.61) | 0.93 |
| CRRT, dose prescribed* | 0.97 (0.96–0.99) | 0.005 |
| Intermittent RRT duration (per hour)** | 1.00 (1.00–1.00) | 0.06 |

HR=hazard ratio; RRT=renal replacement therapy; CRRT=continuous renal replacement therapy; IHD=intermittent hemodialysis; SLED – sustained low efficiency dialysis; IV=intravenous; SOFA=sequential organ failure assessment; SAPS=simplified acute physiology score

*Only patients that received CRRT as initial RRT modality included

**Only patients that received IHD or SLED as initial RRT modality included

Sensitivity analysis: baseline characteristics and outcomes of the STARRT-AKI cohort according to the occurrence of no HAE, 1 HAE or > 1 HAE

We also performed a sensitivity analysis to compare the characteristics, treatments and outcomes of patients with > 1 HAE, compared to those who experienced no HAE, as well as those who experienced just 1 HAE (Table 5). Patients who experienced multiple HAE were significantly more likely to have received the accelerated RRT randomisation strategy and were more likely to have had IHD or SLED as their initial RRT therapy. They also had higher SOFA and SAPS II scores at randomisation and were more likely to have experienced sepsis in previous 72 h. They were more likely to be mechanically ventilated

Table 3 Multivariable Cox proportional hazards model based on the least absolute shrinkage and selection operator (LASSO) with time to haemodynamic adverse event as the dependent variable

| | HR (95% CI) | P-value |
|--|------------------------|---------|
| Anti-coagulation (ref. regional citrate) | | |
| IV heparin | 1.23 (0.88–1.73) | 0.23 |
| None | 1.44 (1.02–2.01) | 0.036 |
| Other | 0.81 (0.29–2.23) | 0.68 |
| Initial RRT modality (ref. CRRT) | | |
| IHD | 1.72 (1.27–2.35) | <0.001 |
| SLED | 2.41 (1.48–3.92) | <0.001 |
| SOFA score at RRT initiation | 1.06 (1.01–1.11) | 0.015 |
| Vasoactive medication at RRT initiation | 1.43 (1.00–2.05.00.05) | 0.053 |
| Serum potassium at RRT initiation | 1.13 (0.94–1.34) | 0.18 |
| Fluid balance at RRT initiation | 1.01 (0.99–1.03) | 0.2 |
| Chronic kidney disease | 0.89 (0.68–1.16) | 0.39 |
| Sepsis | 1.03 (0.78–1.35) | 0.84 |
| Diabetes mellitus | 1.17 (0.89–1.55) | 0.26 |

HR=hazard ratio; RRT=renal replacement therapy; CRRT=continuous renal replacement therapy; IHD=intermittent hemodialysis; SLED – sustained low efficiency dialysis; SOFA=sequential organ failure assessment; SAPS=simplified acute physiology score

and on vasoactive medications at the time of randomisation and had a higher cumulative fluid balance both at randomisation and at RRT initiation as well. Patients who experienced multiple HAE also had a significantly lower systolic blood pressure at the time of randomisation. In an unadjusted analysis of the effect of > 1 HAE on patient outcomes, there was an increased risk of all-cause mortality at 90 days associated with experiencing > 1 HAE (Table 6). There were also significantly fewer vasoactive-free and ventilator-free days at 28 days associated with > 1 HAE. However, in a multivariate analysis, which was adjusted by baseline and RRT initiation covariates, there remained an increased risk of all-cause mortality at 90 days associated with > 1 HAE, but no significant association with any other clinical outcomes.

Discussion

Key findings

In this secondary analysis of the multinational STARRT-AKI trial, we assessed factors associated with the occurrence of HAE among participants in the trial and whether these HAE were associated with clinical outcomes. In a multivariable Cox proportional hazards model, IHD or SLED as the initial RRT modality, no anticoagulation for CRRT, and SOFA score at RRT initiation, respectively, were found to be associated with time to HAE. However, in a multivariable analysis which was adjusted by baseline and RRT initiation covariates, there was no significant association between HAE and patient mortality, dialysis dependence, length of stay, RRT-free days, ventilator-free days and vasoactive-free days. Patients experiencing > 1

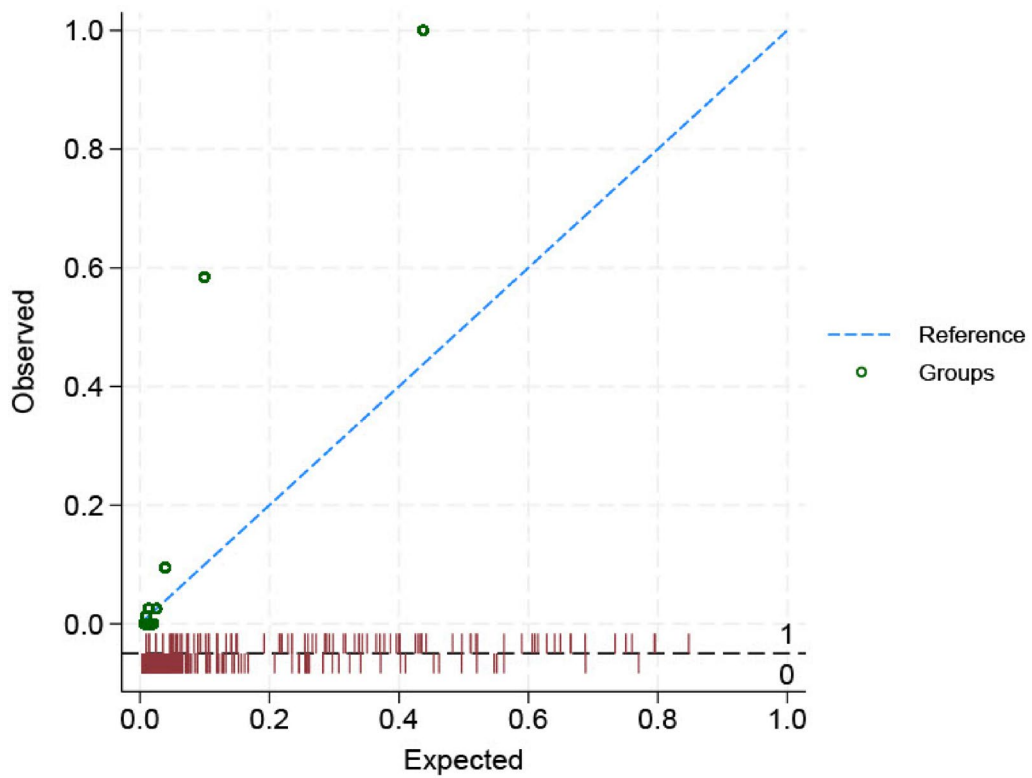


Fig. 2 Calibration plot for observed vs. expected results using the Lasso model

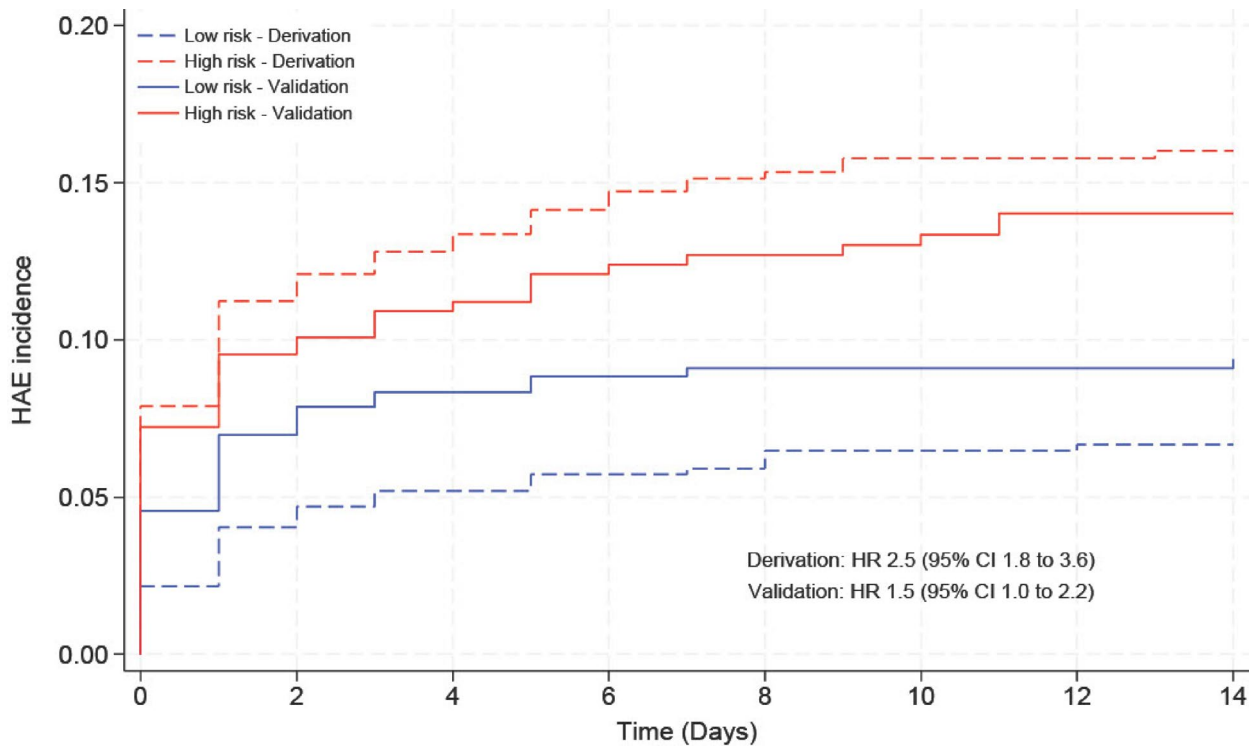


Fig. 3 Kaplan-Meier curve of haemodynamic adverse event incidence according to high-risk versus low-risk groups based on cut-off values from the LASSO model

Table 4 Multivariate analysis* (unadjusted and adjusted) of the association between haemodynamic adverse events during RRT and patient outcomes

| | Unadjusted | | Adjusted | |
|---------------------------------|------------------------|---------|-----------------------|---------|
| | OR or MD (95% CI) | P-value | OR MD (95% CI) | P-value |
| All-cause mortality at 90 days | 1.39 (1.06–1.82) | 0.018 | 1.22 (0.90–1.64) | 0.19 |
| RRT dependence at 90 days | 1.31 (0.71–2.43) | 0.39 | 1.51 (0.79–2.88) | 0.21 |
| ICU length of stay | 0.06 (–1.70 to 1.82) | 0.95 | –0.45 (–2.18 to 1.28) | 0.61 |
| Hospital length of stay | –1.14 (–4.41 to 2.12) | 0.49 | –1.61 (–4.87 to 1.66) | 0.34 |
| Vasoactive-free days at 28 days | –2.62 (–4.24 to –1.00) | 0.002 | –1.40 (–2.88 to 0.08) | 0.06 |
| Ventilator-free days at 28 days | –2.26 (–3.81 to –0.72) | 0.004 | –0.66 (–2.05 to 0.72) | 0.35 |

OR=odds ratio; MD=mean difference; ICU=intensive care unit; RRT=renal replacement therapy.

*The variables included in this multivariable model were age, sex, weight, pre-existing chronic kidney disease (CKD), hypertension, diabetes mellitus, heart failure, coronary artery disease, liver disease, sepsis, septic shock, Simplified Acute Physiology score II (SAPS II), Sequential Organ Failure Score (SOFA) score, mechanical ventilation, vasoactive support, serum potassium, serum bicarbonate, median cumulative fluid balance, treatment allocation, RRT modality, IHD and CRRT parameters including blood flow rate, ultrafiltration rate, CRRT dose, anticoagulation and IHD/SLED duration

HAE did, however, show increased risk for all-cause mortality at 90 days in a sensitivity analysis.

Relationship to previous studies

Our findings are consistent with previous studies that implied HAE events result from a number of mechanisms, including decreased cardiac output and decreased peripheral resistance [15, 16]. Risk factors such as an increased baseline SAPS II score and an increased SOFA score, receipt of mechanical ventilation, receipt of vasoactive medication and cumulative fluid balance at RRT initiation are likely all surrogate markers for illness severity and potential states of reduced cardiac output and/or peripheral vascular resistance, so it is unsurprising that these should be associated with increased risk of HAE. The relationship between use of no anticoagulation during CRRT and HAE has not previously been described, but could act as an indirect marker for illness severity and may also relate to blood loss due to extracorporeal circuit clotting in the absence of anticoagulation [17]. The decision not to use anti-coagulation for CRRT is usually related to active bleeding or high bleeding risk, which also puts patients at higher risk of HAE.

HAE events remain commonly reported during IHD and SLED as RRT treatment modalities for critically ill patients [16, 18]. CRRT continues to be favoured as an initial RRT treatment modality in haemodynamically unstable ICU patients or those who are deemed at risk of haemodynamic instability during treatment [19]. A

secondary analysis of the STARRT-AKI trial similarly found that initial receipt of CRRT was associated with a lower risk of death or RRT dependence at 90-days compared to initial receipt of IHD [20]. However, HAE has also been noted during studies of CRRT [21, 22], with one study noting that HAE was more common during CRRT for patients who demonstrated preload dependence prior to commencing treatment [23].

Our finding that a single HAE was not associated with patient outcomes, including mortality, dialysis dependence, length of stay, RRT-free days, ventilator-free days and vasoactive-free days, differs from previous studies which have shown an association between HAE and in-patient mortality [8], as well as a potential for lower rates of resolution of AKI and renal recovery [9]. There are several reasons why these relationships may not have been observed. One possibility is that there is no detectable biological relationship between HAE and patient outcomes. The definition of HAE used in the study may not have been sensitive or specific enough to correlate with harm. The lack of a standard definition for HAE is a significant general limitation to progress in this area. Another possibility is that the relationship is confounded by illness severity, which is included in the models. Additionally, most HAE events occurred early and may therefore have been too temporally removed from the outcomes that are being modelled. However, our sensitivity analysis did show a significant association between >1 HAE and all-cause mortality at 90 days, reflecting the higher overall illness severity associated with patients who experienced >1 of these events.

Implications of study findings

Our study confirms that risk factors for HAE in the ICU include markers of increased illness severity such as SAPS II score, SOFA score and mechanical ventilation, as well as a pre-existing receipt of vasopressor medications. Use of IHD or SLED as the initial RRT modality for critically ill patients was associated with an increased risk of HAE, as per previous studies, and highlights the need for increased caution when using either of these intermittent RRT modalities as initial treatments in the ICU, along with strategies to mitigate HAE events, particularly for patients with baseline haemodynamic instability or high illness severity scores. Of note, there was a relative paucity of SLED use in this trial ($n=93$ in Table 1), so this effect may have been exaggerated. Similarly, the accelerated-strategy patients may have been predisposed to greater risk for HAE due to earlier exposure to RRT in the course of their critical illness and resuscitation, whereas patients allocated to the standard-strategy may have benefited from ongoing resuscitation and stabilisation, which may have reduced the risk for subsequent HAE upon RRT initiation. The standard-strategy group

Table 5 Baseline characteristics of patients according to whether they experienced no haemodynamic adverse event, 1 haemodynamic adverse event or >1 haemodynamic adverse event (HAE)

| Characteristic | No HAE n = 2742 | 1 HAE n = 190 | >1 HAE n = 60 | P-value |
|--|--------------------|------------------|------------------|---------|
| IRRT strategy (%) | | | | 0.001 |
| Accelerated | 49.2 | 60 | 65 | |
| Standard | 50.8 | 40 | 35 | |
| Initial RRT (%) | | | | <0.001 |
| CRRT | 70.9 | 57.4 | 56.7 | |
| IHD | 25.3 | 34.7 | 33.3 | |
| SLED | 3.9 | 7.9 | 10.0 | |
| Age (years) | 64.6 (13.9) | 65.1 (13.4) | 64.2 (13.3) | 0.89 |
| Body weight (kg) | 87.4 (25.6) | 90.7 (26.8) | 83.4 (29.1) | 0.11 |
| Female sex (%) | 32.1 | 33.7 | 26.7 | 0.62 |
| Baseline sCr, mg/dl, SD | 1.4 (1.0) | 1.3 (0.8) | 1.3 (0.8) | 0.49 |
| Baseline eGFR, ml/min/1.73 m ² , SD | 66.2 (30.1) | 67.5 (30) | 67.4 (24.9) | 0.82 |
| Pre-existing conditions | | | | |
| Chronic kidney disease (%) | 44.4 | 44.7 | 31.7 | 0.14 |
| Hypertension (%) | 55.7 | 55.3 | 55 | 0.99 |
| Diabetes mellitus (%) | 30.4 | 32.6 | 31.7 | 0.77 |
| Heart failure (%) | 13.7 | 16.3 | 13.3 | 0.58 |
| Coronary artery disease (%) | 22.3 | 20.5 | 13.3 | 0.23 |
| Liver disease (%) | 11.3 | 12.6 | 10 | 0.81 |
| Characteristics at randomisation | | | | |
| SOFA score, SD | 11.6 (3.6) | 12.8 (3.7) | 12.6 (3.3) | <0.001 |
| SAPS II score, SD | 58.3 (17.5) | 62.8 (16) | 61.7 (14.5) | 0.001 |
| SCr at randomization, mg/dl, SD | 3.5 (1.7) | 3.5 (1.6) | 3.4 (1.2) | 0.81 |
| Cardiopulmonary bypass (%) | 7.5 | 11.1 | 10 | 0.16 |
| Aortic aneurysm repair (%) | 4.7 | 4.7 | 11.7 | 0.063 |
| Other vascular surgery (%) | 5.2 | 5.3 | 3.3 | 0.94 |
| Trauma (%) | 3.9 | 4.7 | 3.3 | 0.82 |
| Sepsis in the last 72 h (%) | 57.2 | 60 | 75 | 0.015 |
| Mechanical ventilation (%) | 75.8 | 85.8 | 85 | 0.002 |
| Vasoactive medication (%) | 69.2 | 78.4 | 85 | <0.001 |
| Cumulative fluid balance at randomization, ml, SD | 3946.2 (5257.5) | 5412.8 (9467.0) | 5350.1 (5244.1) | <0.001 |
| Serum potassium, mmol/L, SD | 4.5 (0.8) | 4.6 (0.8) | 4.7 (0.7) | 0.13 |
| Serum bicarbonate, mmol/L, SD | 19.6 (4.6) | 19.2 (5.1) | 19.4 (4.2) | 0.52 |
| Urine output, ml, SD | 753.2 (882.1) | 607.8 (778.2) | 649 (912.6) | 0.065 |
| Heart rate, bpm, SD | 107.3 (26.6) | 109.5 (25.2) | 108.1 (23.4) | 0.54 |
| Systolic blood pressure, mm Hg, SD | 101.7 (28.3) | 97.1 (26.4) | 91.3 (19.3) | 0.002 |
| Temperature, °C, SD | 37.4 (1.3) | 37.3 (1.4) | 37.5 (1.4) | 0.66 |
| Characteristics at RRT initiation | | | | |
| Cumulative fluid balance at RRT initiation, ml, SD | 5183.7 (6731.5) | 6428.8 (10028.5) | 6484.7 (5906.9) | 0.034 |
| Serum creatinine, mg/dl, SD | 4.1 (2.0) | 4.2 (1.9) | 3.8 (1.6) | 0.29 |
| Serum potassium, mmol/L, SD | 4.5 (0.7) | 4.5 (0.7) | 4.5 (0.7) | 0.4 |
| Serum bicarbonate, mmol/L, SD | 20.1 (4.6) | 19.9 (5.0) | 20.6 (4.2) | 0.56 |

HR = hazard ratio; RRT = renal replacement therapy; CRRT = continuous renal replacement therapy; IHD = intermittent hemodialysis; SLED = sustained low efficiency dialysis; SOFA = sequential organ failure assessment; SAPS = simplified acute physiology score.

received approximately 25 additional hours of resuscitation prior to RRT initiation and had a significantly higher fluid balance at RRT initiation as a result of this. The standard-strategy patients were also able to achieve a higher ultrafiltration volume in their first RRT session, likely as a result of this more prolonged resuscitation time and higher fluid balance at RRT initiation.

The *K* statistic for the Kaplan-Meier curve of patients at high versus low-risk for HAE based on the LASSO model was only 0.60, indicating only a modest discrimination and highlighting the need for better tools to anticipate HAE. We found no significant association between HAE and patient outcomes, which probably relates to the fact that this dataset was not designed to detect this

Table 6 Multivariate analysis* (unadjusted and adjusted) of the association of multiple haemodynamic adverse events during RRT with patient outcomes

| | Unadjusted | | Adjusted | |
|---------------------------------|------------------------|---------|------------------------|---------|
| | OR or MD (95% CI) | P-value | OR or MD (95% CI) | P-value |
| All-cause mortality at 90 days | 2.40 (1.37–4.21) | 0.002 | 2.20 (1.19–4.07) | 0.011 |
| RRT dependence at 90 days | 0.24 (0.01–3.94) | 0.31 | 0.35 (0.02–6.03) | 0.47 |
| ICU length of stay | 0.89 (–2.57 to 4.34) | 0.62 | 0.07 (–3.32 to 3.46) | 0.97 |
| Hospital length of stay | –3.39 (–9.82 to 3.04) | 0.30 | –3.98 (–10.37 to 2.41) | 0.22 |
| Vasoactive-free days at 28 days | –3.84 (–7.04 to –0.65) | 0.019 | –2.27 (–5.18 to 0.63) | 0.12 |
| Ventilator-free days at 28 days | –3.64 (–6.68 to –0.60) | 0.019 | –1.68 (–4.39 to 1.02) | 0.22 |

OR = odds ratio; MD = mean difference; ICU = intensive care unit; RRT = renal replacement therapy

Firth's logistic regression model was used for the analysis of all-cause mortality and RRT dependence due to sparse outcome data for patients with ≥ 2 haemodynamic adverse events

*The variables included in this multivariable model were age, sex, weight, pre-existing chronic kidney disease (CKD), hypertension, diabetes mellitus, heart failure, coronary artery disease, liver disease, sepsis, septic shock, Simplified Acute Physiology score II (SAPS II), Sequential Organ Failure Score (SOFA) score, mechanical ventilation, vasoactive support, serum potassium, serum bicarbonate, median cumulative fluid balance, treatment allocation, RRT modality, IHD and CRRT parameters including blood flow rate, ultrafiltration rate, CRRT dose, anticoagulation and IHD/SLED duration

association and highlights the need for primary trials in AKI-RRT in the ICU with a focus on HAE as the primary outcome. We await the results of ongoing trials such as the ALTER-AKI RCT, which will determine whether randomization to receive hyperoncotic albumin during RRT for critically ill patients with AKI can improve patient outcomes by improving hemodynamic stability during treatment to facilitate fluid removal (Clinicaltrials.gov ID NCT04705896) [24].

Though we did not find a significant association between HAE and adverse patient outcomes in this study, it remains important to avoid HAE where possible and to try to mitigate the risk of this through careful selection of RRT treatment modality, particularly bearing in mind patient illness severity scores and the level of organ support that they currently require, as well as their cumulative fluid balance at the time of RRT initiation.

Strengths and limitations

This secondary analysis has notable strengths. It is one of the largest studies to evaluate potential risk factors for HAE in the ICU in a multinational clinical trial cohort. We were able to use high-quality, rigorously collected international clinical trial data to test our hypotheses. Our statistical analysis was precise and utilized both cause-specific and sub-distribution hazard ratios with

a competing risk for death to minimize the risk of bias associated with performing a secondary survival analysis on clinical trial data.

There are important limitations to consider. This is a secondary analysis involving a subset of clinical trial patients and therefore all results of this can be viewed as hypothesis-generating. HAE was not the primary outcome of the STARRT-AKI trial so therefore the trial was not powered to assess the effect of these adverse events on patient outcomes. As a result, we recognise that this analysis is susceptible to residual confounding. Data were also not available on what manoeuvres or preventative measures were taken in individual patients/centres to mitigate the risk of HAE that may be recommended in clinical practice guidelines, such as use of a lower dialysate temperature, sodium profiling, calcium supplementation, use of albumin and use of a lower ultrafiltration rate, etc. We also did not capture specific data regarding circuit exchanges and downtime so were not able to account for this in our analysis. We also acknowledge that the occurrence of other unmeasured factors such as a subsequent clinical deterioration, new onset sepsis or organ dysfunction, and non-RRT fluid management strategies, e.g. diuretics, may have contributed to HAE during RRT in these critically ill patients. HAE were also assessed and adjudicated by investigators at each site, without a central adjudication committee to systematically confirm the details of these adverse events, so there may have been inconsistent reporting and ascertainment bias associated with this. Moreover, this analysis was conducted within the confines of a clinical trial so the participants may differ systematically from those encountered in routine practice, though the integration of principles of individual clinician equipoise into recruitment for STARRT-AKI helped to reflect “real-world” clinical practice and to reduce bias in this regard [25].

Conclusions

In this secondary analysis of the STARRT-AKI trial, we found that use of both IHD and SLED as initial RRT modality in comparison to CRRT and a higher SOFA score at RRT initiation were significantly associated with time to HAE occurrence. There was no significant association between HAE and adverse clinical outcomes, though patients experiencing > 1 HAE showed increased risk for all-cause mortality at 90 days in a sensitivity analysis. This highlights the need for trials testing strategies that are designed to mitigate hemodynamic instability during the delivery of RRT.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13054-025-05693-0>.

Supplementary Material 1

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Author contributions

YK, BdC, RW and SB designed the study and wrote the main manuscript text. BdC analysed the data and prepared Figs. 1, 2 and 3. WBS, EC, PM and AN edited and reviewed the main manuscript.

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Data availability

De-identified participant data from the STARRT-AKI trial which were used to generate these results will be made available on request via email to the trial co-chairs (SMB and RW).

Declarations

Ethics approval and consent to participate

The STARRT-AKI trial was approved by the health research ethics boards at the University of Alberta (File # Pro00060023), Unity Health Toronto (CTO Project ID: 0761) and the institutional review board at each participating site. Depending on local standards and legislation, informed consent was obtained from patients and substitute decision-makers or through waived consent.

Consent for publication

Depending on local standards and legislation, informed consent for publication was obtained from patients and substitute decision-makers or through waived consent. All authors have given their consent for publication as well.

Competing interests

SMB has received fees from Baxter for scientific advisory and speaking; fees from BioPorto for scientific advisory and clinical adjudication; and fees from Novartis for scientific advisory. RW has received fees from Baxter for scientific advisory and speaking. SMB and RW have received unrestricted grants from Baxter to support the STARRT-AKI trial. PM has received honoraria for consulting from BioPorto, Novartis, Alexion, and CalciMedica. WBS has no conflict to disclose.

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