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ORIGINAL

Initiation of continuous renal replacement therapy versus intermittent hemodialysis in critically ill patients with severe acute kidney injury: a secondary analysis of STARRT-AKI trial

Ron Wald[1*], Stephane Gaudry[2,3], Bruno R. da Costa[4], Neill K. J. Adhikari[5], Rinaldo Bellomo[6,7,8,9], Bin Du[10], Martin P. Gallagher[11], Eric A. Hoste[12], François Lamontagne[13], Michael Joannidis[14], Kathleen D. Liu[15], Daniel F. McAuley[16], Shay P. McGuinness[17], Alistair D. Nichol[18,19], Marlies Ostermann[20], Paul M. Palevsky[21,22], Haibo Qiu[23], Ville Pettilä[24], Antoine G. Schneider[25], Orla M. Smith[26], Suvi T. Vaara[27], Matthew Weir[28], Didier Dreyfuss[3,29] and Sean M. Bagshaw[30] on behalf of the STARRT-AKI Investigators

Abstract

Background: There is controversy regarding the optimal renal-replacement therapy (RRT) modality for critically ill patients with acute kidney injury (AKI).

Methods: We conducted a secondary analysis of the STandard versus Accelerated Renal Replacement Therapy in Acute Kidney Injury (STARRT-AKI) trial to compare outcomes among patients who initiated RRT with either continuous renal replacement therapy (CRRT) or intermittent hemodialysis (IHD). We generated a propensity score for the likelihood of receiving CRRT and used inverse probability of treatment with overlap-weighting to address baseline inter-group differences. The primary outcome was a composite of death or RRT dependence at 90-days after randomization.

Results: We identified 1590 trial participants who initially received CRRT and 606 who initially received IHD. The composite outcome of death or RRT dependence at 90-days occurred in 823 (51.8%) patients who commenced CRRT and 329 (54.3%) patients who commenced IHD (unadjusted odds ratio (OR) 0.90; 95% confidence interval (CI) 0.75–1.09). After balancing baseline characteristics with overlap weighting, initial receipt of CRRT was associated with a lower risk of death or RRT dependence at 90-days compared with initial receipt of IHD (OR 0.81; 95% CI 0.66–0.99). This association was predominantly driven by a lower risk of RRT dependence at 90-days (OR 0.61; 95% CI 0.39–0.94).

Conclusions: In critically ill patients with severe AKI, initiation of CRRT, as compared to IHD, was associated with a significant reduction in the composite outcome of death or RRT dependence at 90-days.

Keywords: Acute kidney injury, Renal-replacement therapy, Modality, Intermittent hemodialysis, Continuous, Mortality, Randomized trial

*Correspondence: waldr@smh.ca
[1] Division of Nephrology, St. Michael's Hospital, University of Toronto, Li Ka Shing Knowledge Institute, Toronto, ON, Canada
Full author information is available at the end of the article

Ron Wald, Stephane Gaudry, Didier Dreyfuss and Sean M. Bagshaw contributed equally to this work.

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Introduction

Critical illness is frequently complicated by acute kidney injury (AKI) and renal-replacement therapy (RRT) remains the cornerstone of support in a significant proportion of patients who develop refractory medical complications or severe persistent AKI [1, 2]. Several aspects of the acute RRT prescription remain controversial, including the most suitable initial RRT modality [3–5]. The most common RRT modalities deployed in intensive care unit (ICU) settings are intermittent hemodialysis (IHD) and continuous renal replacement therapy (CRRT). IHD is generally provided for 3–5 h per session every other day, delivered with a conventional dialysis machine. CRRT is delivered using a specialized platform device continuously over a prolonged (> 24-h) period and involves slower solute clearance and fluid removal [6]. CRRT is generally preferred among critically ill patients with hemodynamic instability, multi-organ failure, and those at risk of or with evidence of cerebral edema (e.g., brain injury, liver failure), whereas IHD is felt to be more suitable for hemodynamically stable patients weaned from vasoactive support, those with acute intoxications with dialyzable toxins; or those with urgent indications for selected metabolic derangements (e.g., refractory hyperkalemia).

Clinical practice guidelines published more than a decade ago suggested that CRRT and IHD are complementary therapies in critically ill patients with AKI. However, those guidelines suggested the preferential use of CRRT for patients with hemodynamic instability and for those with or at increased risk of intracranial hypertension [7, 8]. Meta-analyses [9–12] and previous randomized trials [12–15] have not consistently shown superiority of CRRT compared with IHD in terms of mortality or kidney recovery. However, many of these trials were relatively small and had methodological limitations, including unsuitable sample size estimations, in-trial protocol amendments, prolonged accrual time, premature trial termination, differences in baseline characteristics, post-randomization exclusions, protocol violations and treatment crossover, and exclusion of patients with hemodynamic instability or inclusion of patients with relatively low illness acuity. In addition, emerging observational data and secondary analyses from randomized trials suggest that the initial RRT modality may influence clinical outcomes [16–18]. There remains clinical uncertainty with respect to the optimal selection of RRT modality for critically ill patients with AKI.

Accordingly, we conducted a secondary analysis of the STandard vs Accelerated initiation of Renal Replacement Therapy in Acute Kidney Injury (STARRT-AKI) trial to evaluate whether the initial RRT modality prescribed to critically ill patients with severe AKI was associated with differential patient-centered clinical outcomes.

Take-home message

The optimal modality for the delivery of renal replacement therapy (RRT) to critically ill patients with acute kidney injury is controversial. We performed a retrospective analysis of the STARRT-AKI trial and found that continuous renal replacement therapy was associated with a lower risk of the composite of all-cause mortality or RRT dependence 90 days after randomization.

Methods

Design

This is a post-hoc secondary analysis of the STARRT-AKI trial (Data Creation Plan available at: https://www.ualberta.ca/critical-care/research/current-research/starrtaki/documents.html). The STARRT-AKI trial randomized 3019 critically ill patients with severe AKI to two strategies for RRT initiation, accelerated or standard. The trial recruited patients at 168 sites in 15 countries between October 2015 and September 2019 [19].

The STARRT-AKI trial was approved by the Research Ethics Boards at Unity Health Toronto (CTO 16–009), the University of Alberta (File # Pro00060023) and all participating sites. Depending on local standards and legislation, informed consent was obtained from patients and substitute decision-makers or the need for informed consent was deferred or waived.

The design and main outcomes of the STARRT-AKI trial have been reported [19–21]. Briefly, critically ill patients with severe AKI (categorized as stage 2 or 3 by the Kidney Disease: Improving Global Outcomes [KDIGO] classification [8]) with no urgent indications for RRT were randomly allocated to an accelerated- or standard-strategy for RRT initiation. After fulfilling eligibility, participants allocated to the accelerated-strategy were to start RRT within 12 h, whereas in participants allocated to the standard-strategy, clinicians were discouraged from starting RRT unless one or more conventional indications developed or if AKI persisted for > 72 h [19].

To align with published clinical practice guidelines and contemporary practice, the trial protocol and operations manual suggested that clinicians initially use CRRT or sustained low efficiency dialysis (SLED, defined as intermittent therapy typically delivered over 6–12 h) for patients with hemodynamic instability (Available at: https://www.ualberta.ca/critical-care/research/current-research/starrtaki/documents.html) [8]. However, clinicians were given ultimate discretion regarding the initial RRT modality selection as well as all other aspects of the RRT prescription [21].

Population

Participants analyzed in the modified intention-to-treat analysis of the STARRT-AKI trial and who received at least one session of RRT, either CRRT or IHD, were eligible for inclusion in this secondary analysis. We excluded participants whose initial RRT modality was SLED, as it was used infrequently.

Exposure

The primary exposure was the initial RRT modality, defined as CRRT or IHD. Since RRT modalities are sometimes delivered in an integrated fashion, we also evaluated the proportion of days on RRT in the ICU (occurring during the first 14 days from randomization) during which CRRT was deployed. Proportion of CRRT days was evaluated as a continuous variable and categorized into 20% increments.

Outcomes

The primary outcome was a composite of all-cause mortality or RRT dependence 90 days after randomization. Investigators were asked to designate participants as "RRT dependent" if they received any form for RRT within 7 days of day 90 following randomization Secondary outcomes were the components of the primary outcome, ventilator-free days, vasoactive-free days, and ICU-free days (all at 28 days), ICU length of stay, hospital length of stay, and hospital-free days at 90 days. A "free" day was defined as < 2 h of organ support or time in the ICU or hospital on that calendar day. Participants who died before the free-day landmark (28- or 90-days, depending on the outcome) were assigned 0 free-days [22].

Statistical analyses

We compared baseline variables between patients initiating CRRT or IHD using numbers (%) for categorical variables and means (standard deviation) or medians (interquartile range) for continuous or count variables. We accounted for missing baseline and outcome data by using multiple imputation with pre-treatment and outcome variables as explanatory variables in the imputation model, to create 20 imputed datasets [23–25] (Supplementary Table 1). We used Rubin's rules to calculate the standard errors of estimates derived from the imputed datasets to account for the uncertainty associated with the imputation of missing values. There were no missing data for mortality at 90-days but information on RRT dependence at 90-days was missing for 11 participants (6 who initiated CRRT and 5 who initiated IHD). The multiple imputation model included both pre-treatment and outcome variables as previously recommended for propensity score analysis with missing pre-treatment data [24]. Following multiple imputation, we estimated propensity scores for initial receipt of CRRT using a probit model that included pre-treatment variables considered to be associated with outcomes as explanatory variables [26] (Supplementary Table 1). Propensity scores were calculated separately for each imputed dataset [24, 27]. We then used propensity scores to generate overlap weights and inverse probability of treatment weights (IPTW) [22, 26–29]. The pre-specified main analysis of the primary and secondary outcomes was based on logistic or linear regression models using overlap weighting. Overlap weighting was used in the main analysis as it overcomes some of the IPTW limitations, such as exclusion of participants from the analysis due to extreme IPTW values, resulting in better performance in terms of bias and precision [22, 27, 28]. Moreover, overlap weighting focuses on patients where there is most clinical equipoise with regards to receipt of CRRT vs IHD, yielding treatment effects that are more useful in a real clinical setting. We conducted pre-specified subgroup analyses (allocated RRT strategy; age; sex; chronic kidney disease [CKD] status; sepsis; mechanical ventilation; vasoactive support; Sequential Organ Failure Assessment (SOFA) score [baseline and at RRT initiation]; cumulative fluid balance at RRT initiation) of the primary outcome accompanied by interaction tests using logistic regression models with overlap weighting with a p value < 0.05 defining evidence of a significant interaction. To assess the robustness of the main analysis of the primary outcome, we conducted sensitivity analyses using IPTW with trimming at the 1 and 99 percentiles of the propensity score distribution before calculating IPTWs, truncation of IPTW at 1 and 99 percentiles, and IPTW without trimming or truncation [27, 30]. We presented group-specific overlap weighting adjusted pre-treatment characteristics and conducted unadjusted analyses to assess the reduction of confounding by indication achieved with the use of propensity scores [26]. For analyses in which the exposure was the proportion of days on CRRT, we evaluated the relationship between the exposure and the outcomes of interest using logistic regression with adjustment for all variables included in the aforementioned propensity scores.

We performed three pre-specified sensitivity analyses of the primary outcome including: limiting the cohort to patients who only received a single modality of RRT (CRRT or IHD); limiting the cohort to patients who received vasoactive support at RRT initiation; and limiting the cohort to patients who received a minimum of 3-days of RRT. All analyses were performed using Stata version 15.1 (StataCorp LLC, College Station, TX).

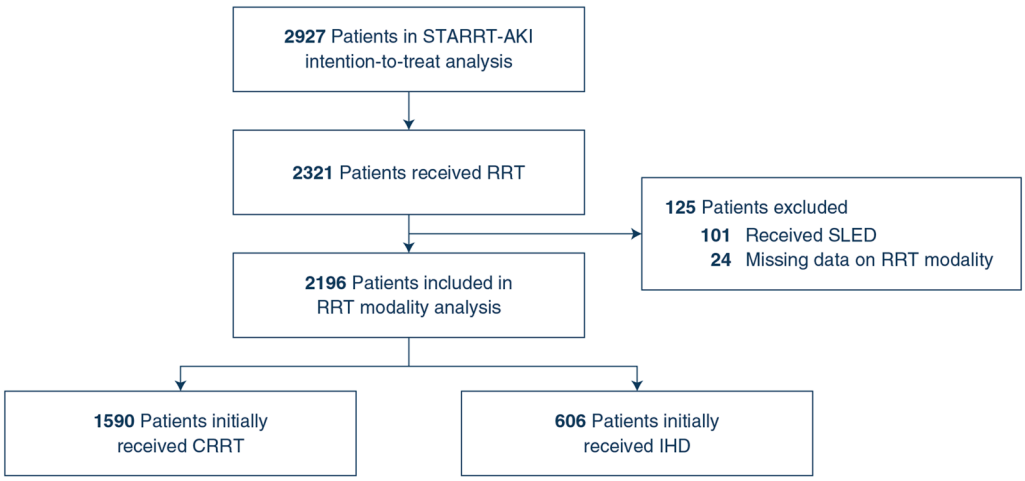

Fig. 1 Assembly of the study cohort, stratified by initial receipt of CRRT or IHD. *CRRT* continuous renal replacement therapy, *IHD* intermittent hemodialysis, *RRT* renal replacement therapy, *SLED* sustained low efficiency dialysis

Results

Patients

Among 2927 participants in the modified intention-to-treat analysis, 2321 received RRT (1418 allocated to the accelerated-strategy and 903 allocated to the standard-strategy). We excluded 24 participants with missing data on initial modality and 101 participants who initiated SLED. Of the remaining 2196 participants, 1590 (72.4%) initially received CRRT and 606 (27.6%) received IHD (Fig. 1).

Patients who initially received CRRT were younger; less likely to have pre-existing CKD, diabetes mellitus, hypertension, and heart failure; had higher SAPS II and SOFA scores; and were more likely to be receiving mechanical ventilation and vasoactive support, compared to patients initially receiving IHD (Table 1). At the time of RRT initiation, CRRT recipients had higher urine output, lower serum creatinine and lower cumulative fluid balance compared to those who received IHD. Following overlap weighting, CRRT and IHD groups were well balanced (Table 1). Information on missing data is found in Supplementary Table 2.

Primary outcome

The composite primary outcome of death or RRT dependence at 90-days occurred in 823 (51.8%) patients who initially started CRRT and 329 (54.3%) who initially started IHD (unadjusted odds ratio (OR) 0.90; 95% confidence interval (CI) 0.75–1.09). After inverse probability overlap weighting with a propensity score for the initial receipt of CRRT, receipt of CRRT was associated with a lower risk of the composite of death or RRT dependence at 90-days compared with initial receipt of IHD (OR 0.81; 95% CI 0.66–0.99). Results of analyses by IPTW alone as well as with trimming and truncation, respectively, are shown in Supplementary Table 3.

Subgroup analyses

The association between initial RRT modality and the composite of death or RRT dependence at 90-days was evaluated across 10 pre-specified subgroups, including the randomly allocated RRT initiation strategy (Fig. 2). There were no statistically significant interactions.

Secondary outcomes

All-cause mortality at 90-days occurred in 752 (47.3%) patients who initially received CRRT and 279 (46.0%) patients who initially received IHD (unadjusted OR 1.05, 95% CI 0.87–1.27; OR after overlap weighting, 0.90; 95% CI 0.74–1.11) (Table 2). Patients who commenced CRRT had a lower risk of RRT dependence at 90-days compared with those who commenced IHD (unadjusted OR 0.51, 95% CI 0.35–0.76; OR after overlap weighting, 0.61; 95% CI 0.39–0.94). There were no statistically significant differences in ICU and hospital length of stay between patients who initially received CRRT compared with IHD. However, patients who initially received CRRT had more ICU-free days at 28-days and hospital-free days at 90-days compared to those who commenced IHD (Table 2). Initial RRT modality was not associated with significant differences in ventilator- or vasoactive-free days at 28-days.

Table 1 Patient characteristics at trial randomization and RRT initiation before and after overlap weighting

Characteristics	Crude			Overlap weights		
	CRRT ($n=1590$)	IHD ($n=606$)	SD	CRRT ($n=1590$)*	IHD ($n=606$)*	SD
Age, years	63.7 (14.3)	65.9 (13.4)	−0.16	65.5 (13.8)	65.4 (13.4)	0.00
Body weight, kg	87.6 (26.4)	87.7 (25.1)	0.00	86.8 (25.9)	87 (24.9)	−0.01
Female sex	508 (31.9)	189 (31.2)	−0.02	506 (31.8)	192 (31.7)	0.01
Baseline serum creatinine, mg/dl	1.3 (1)	1.4 (1.1)	−0.11	1.4 (1.2)	1.4 (1.1)	0.00
Baseline GFR, ml/min/1.73 m^2	67.8 (30)	63.6 (29.9)	0.14	64.8 (30.3)	64.8 (30)	0.00
Pre-existing conditions						
Chronic kidney disease	667 (41.9)	295 (48.7)	−0.14	737 (46.4)	282 (46.6)	0.00
Hypertension	859 (54)	357 (58.9)	−0.10	912 (57.4)	348 (57.4)	0.00
Diabetes mellitus	470 (29.6)	195 (32.2)	−0.06	495 (31.1)	189 (31.2)	0.00
Heart failure	198 (12.5)	96 (15.8)	−0.10	230 (14.5)	88 (14.5)	0.00
Liver disease	200 (12.6)	63 (10.4)	0.07	176 (11.1)	68 (11.2)	0.00
Characteristics at randomization						
SOFA score	12.2 (3.5)	11.4 (3.6)	0.21	12.2 (3.3)	12.2 (3.3)	−0.01
SAPS II score	60.7 (17.2)	57.2 (16.9)	0.20	58.1 (16.7)	58.1 (17.1)	0.00
Serum creatinine, mg/dl	3.4 (1.7)	4 (1.7)	−0.33	3.8 (2)	3.8 (1.7)	0.00
Hemoglobin, g/L	99.8 (22.9)	98.6 (24.1)	0.05	99.4 (23)	99.3 (24.6)	0.00
Serum urea, mmol/L	20.3 (10.7)	23.4 (11.6)	−0.27	22.8 (11.8)	22.7 (11.3)	0.00
Cardiopulmonary bypass in preceding 7 days	140 (8.8)	30 (5)	0.15	96 (6)	36 (5.9)	0.00
Aortic aneurysm repair in preceding 7 days	86 (5.4)	21 (3.5)	0.09	60 (3.8)	23 (3.8)	0.00
Other vascular surgery in preceding 7 days	83 (5.2)	30 (5)	0.01	81 (5.1)	31 (5.1)	0.00
Trauma in preceding 7 days	63 (4)	24 (4)	0.00	59 (3.7)	23 (3.8)	0.00
Sepsis in the last 72 h	922 (58)	374 (61.7)	−0.08	954 (60)	364 (60.1)	0.00
Mechanical ventilation	1275 (80.2)	447 (73.8)	0.15	1187 (74.7)	452 (74.6)	0.00
Vasoactive medication	1224 (77)	347 (57.3)	0.43	1013 (63.7)	386 (63.7)	0.00
Cumulative fluid balance at randomization, mL	4054.5 (5766)	4811.2 (6535.3)	-0.11	4441.8 (7085.3)	4446.8 (6063.1)	0.00
Characteristics at RRT initiation						
Time from ICU admission to RRT initiation, hours	96 (289.9)	111.5 (170.7)	−0.07	108.6 (342.6)	106.8 (179.6)	0.01
Days from hospital admission to RRT initiation	8.9 (16.3)	9.7 (13.5)	−0.06	9.7 (18.9)	9.6 (14.1)	0.00
SOFA score components						
—Respiratory	2.2 (1.1)	1.9 (1.1)	0.26	2.5 (1.2)	2.5 (1.2)	−0.01
—Coagulation	1.1 (1.1)	0.9 (1.1)	0.11	1.1 (1.3)	1.1 (1.3)	0.00
—Liver	0.9 (1.1)	0.7 (1.1)	0.13	0.7 (1.1)	0.7 (1.1)	−0.01
—Cardiovascular	2.6 (1.6)	1.8 (1.8)	0.47	1.2 (1.2)	1.1 (1.1)	0.00
—Central nervous system	2.3 (1.6)	1.8 (1.6)	0.33	1.1 (1.2)	1.3 (1.3)	0.00
—Renal	2.8 (0.9)	3.2 (0.8)	−0.46	1.1 (1.2)	1.1 (1.2)	−0.01
Total SOFA score	11.8 (3.6)	10.4 (3.6)	0.41	10.8 (3.6)	10.8 (3.6)	−0.01
Urine output in preceding 24 h	804.3 (990.5)	649.4 (813.7)	0.17	696.6 (823)	689.9 (850.4)	0.01
Cumulative fluid balance at RRT initiation	4873.9 (6417.9)	6574.1 (8403.1)	−0.22	5633.7 (7915.8)	5654.1 (7025.4)	0.00
Serum creatinine, mg/dL	3.9 (1.9)	4.7 (2.1)	−0.42	4.4 (2.2)	4.4 (2)	0.00
Serum urea, mmol/L	23.9 (18.9)	27.4 (13.8)	−0.23	26.1 (21.2)	26.1 (15)	0.00
Serum potassium, mmol/L	4.5 (0.7)	4.4 (0.7)	0.14	4.4 (0.7)	4.4 (0.7)	0.01
Bicarbonate, mmol/L	20.2 (4.7)	20 (4.1)	0.05	20 (4.7)	20 (4.2)	0.00
pH at RRT initiation	7.3 (0.1)	7.3 (0.1)	−0.03	7.3 (0.1)	7.3 (0.1)	0.00
Hemoglobin, g/L	97.4 (33.3)	95.8 (21.7)	0.06	96.7 (25.7)	96.6 (22.6)	0.00

Continuous variables expressed as mean (standard deviation); categorical variables expressed as number (%)

SD standardized difference, *RRT* renal replacement therapy, *CRRT* continuous renal replacement therapy, *IHD* intermittent hemodialysis, *GFR* glomerular filtration rate, *SOFA* Sequential Organ Failure Assessment, *SAPS* Sepsis Acute Physiology Score, *ICU* intensive care unit

§ Vasoactive support was defined as receipt of any dose of norepinephrine, epinephrine, vasopressin, levosimendan, dobutamine, milrinone, or phenylephrine

* All patients were included in the analyses using overlap weighting. The number of observations in the pseudo-population based on overlap weighting was 373 in the CRRT group and 373 in the IHD group

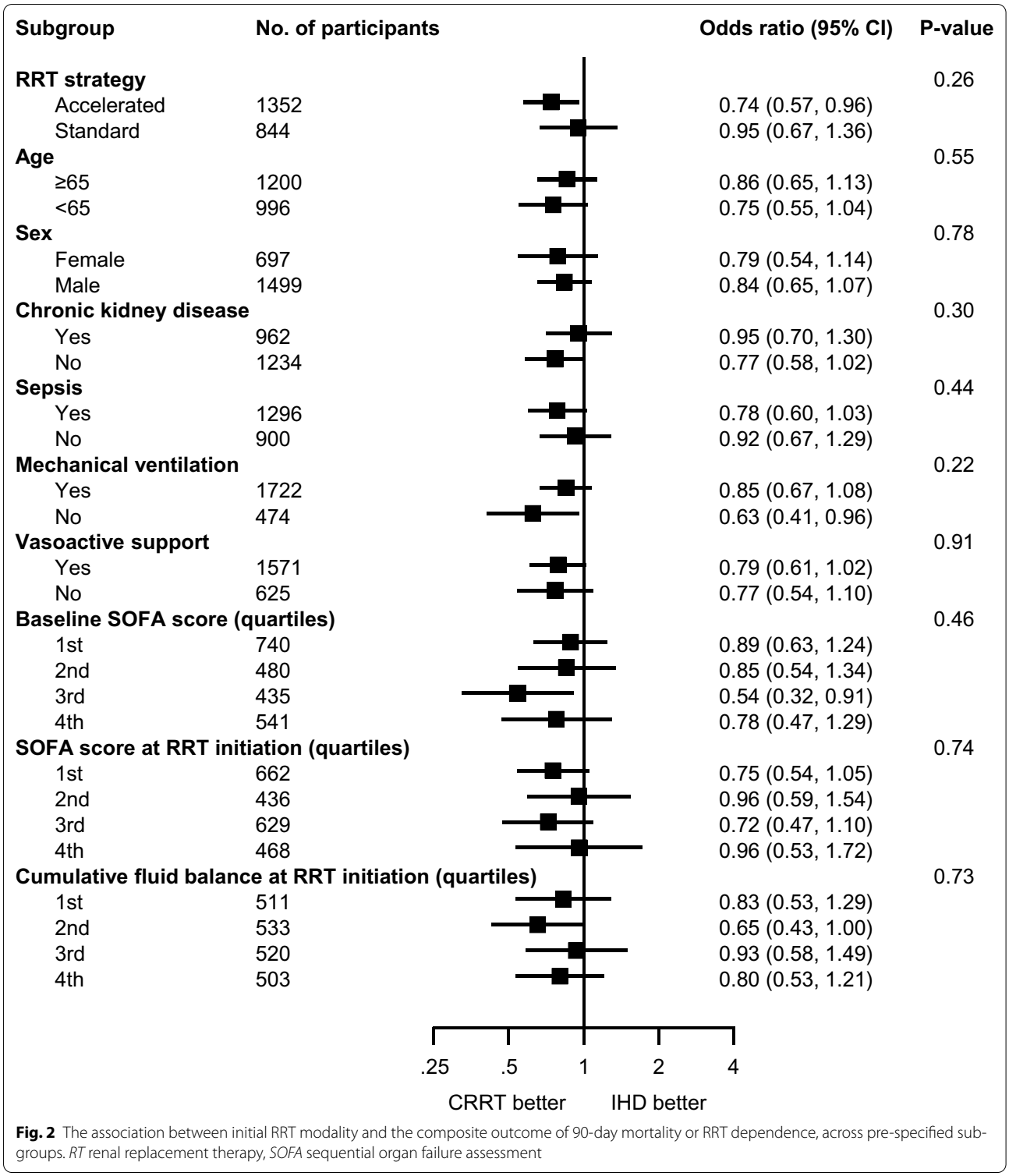

Fig. 2 The association between initial RRT modality and the composite outcome of 90-day mortality or RRT dependence, across pre-specified subgroups. *RT* renal replacement therapy, *SOFA* sequential organ failure assessment

Sensitivity analyses

The initial RRT modality was not associated with the composite of death or RRT dependence at 90-days in sensitivity analyses that restricted the patient cohort in two different ways: those who exclusively received CRRT or IHD through the first 14 days while in ICU and those who were receiving vasoactive support at the time of RRT initiation (Supplementary Table 4). In a further

Table 2 The association between initial RRT modality and primary and secondary outcomes

	Number of patients available for analysis				OR or MD Overlap weighting (95% CI)	*p* value
	CRRT	IHD	CRRT	IHD		
Primary outcome						
Death or RRT dependence at 90-days, n (%)	1590	606	823 (51.8)	329 (54.3)	0.81 (0.66 to 0.99)	0.044
Secondary outcomes						
All-cause mortality at 90 days, n (%)	1590	606	752 (47.3)	279 (46)	0.90 (0.74 to 1.11)	–
RRT dependence at 90 days (survivors only), (n (%))	838	327	71 (8.4)	50 (15.2)	0.61 (0.39 to 0.94)	–
ICU length of stay, days	1590	606	12 (5 to 36)	17 (7 to 165)	− 16.8 (− 34.3 to 0.7)	–
Hospital length of stay, days	1590	606	27 (10 to 81)	40 (15 to 166)	− 14.8 (− 32 to 2.5)	–
ICU-free days at 28 days, median (IQR)	1590	606	0 (0 to 17)	0 (0 to 17)	2 (1 to 3)	–
Hospital-free days at 90 days, median (IQR)	1590	606	0 (0 to 56)	0 (0 to 41)	6.6 (3.1 to 10)	–
Ventilator-free days at 28 days, median (IQR)	1590	606	15 (0 to 23)	17 (0 to 25)	0.4 (− 0.8 to 1.6)	–
Vasoactive-free days at Day 28, median (IQR)	1590	606	20 (0 to 25)	24 (0 to 27)	− 0.7 (− 1.9 to 0.5)	–

RRT renal replacement therapy, *CRRT* continuous renal replacement therapy, *IHD* intermittent hemodialysis, *ICU* intensive care unit, *OR* odds ratio, *MD* mean difference

sensitivity analysis restricting the cohort to patients who received a minimum of 3 days of RRT, initial receipt of CRRT was associated with a lower risk of death or RRT dependence at 90-days (overlap weighting OR 0.63; 95% CI 0.48–0.83).

The association between the proportion of time exposed to CRRT and principal outcomes

The proportion of time spent on CRRT, evaluated in increments of 10%, was not associated with the composite outcome of death or RRT dependence at 90 days (OR 0.99; 95% CI 0.97–1.02) but was associated with a lower risk of RRT dependence at 90 days (0.94, 95% 0.9–0.98). The association between time on CRRT, evaluated in discrete categories, and clinical outcomes is displayed in Supplementary Table 5.

Discussion

In this secondary analysis of the STARRT-AKI trial, we found that CRRT, when used as the initial RRT modality for critically ill patients with severe AKI, was associated with a lower adjusted risk of death or RRT dependence at 90-days compared to initial therapy with IHD. The association was driven by a lower risk of RRT dependence at 90-days among trial participants who commenced CRRT that was also observed when exposure to CRRT was expressed as a proportion of time spent on RRT. We did not find significant heterogeneity in treatment effect across pre-specified subgroups, including allocation to either accelerated or standard RRT initiation. We also found that patients who were initially treated with CRRT had more ICU-free and hospital-free days when compared to those who were initially treated with IHD.

The current analysis provides new information on the relationship between initial RRT modality prescribed to critically ill patients with severe AKI and key patient outcomes. Our findings are aligned with prior randomized trials and meta-analyses in which mortality among critically ill patients randomly allocated to receive either CRRT or IHD was mostly not significantly different [10, 11, 13, 15, 31]. An exception was a study published by Mehta et al. of 166 critically ill patients with a high prevalence of liver failure and found a higher hospital mortality with CRRT when compared with IHD [13].

One of the putative benefits attributed to CRRT is the ability to deliver slow solute clearance and ultrafiltration, while minimizing the risk of hypotension and the potential for secondary kidney and non-kidney organ injury [32]. In STARRT-AKI, initial therapy with CRRT was associated with a 39% relative reduction in the odds of RRT-dependence at 90 days compared with IHD. This suggests that, while pre-morbid disease and acute illness severity are key risk factors for death at 90-days, the choice of initial RRT modality may be of importance for kidney recovery to RRT independence. These findings align with large population-level studies showing that initial therapy with CRRT was associated with greater long-term independence from dialysis [16, 18, 33]. In a recent cross-study patient-level analysis of 2542 patients enrolled in the ATN and RENAL trials [34], the initial receipt of CRRT was associated with reduced RRT dependence at 28-days and more RRT-free days among survivors. In contrast, a recent pooled analysis of the AKIKI and IDEAL-ICU trials that included 543 critically ill patients treated in French ICUs allocated to the early RRT initiation strategy in those trials found that initial

receipt of CRRT was associated with higher mortality at 60-days and no difference in RRT dependence compared with initial receipt of IHD [17].

Some have argued that the higher costs associated with the delivery of CRRT, and the absence of a survival benefit with this modality, justify the preferential utilization of intermittent RRT modalities in ICU settings [35–38]. However, costs are highly variable across health jurisdictions [39] and CRRT may be cost-effective if associated with long-term reductions in chronic dialysis dependence [37, 38, 40]. A suitably designed randomized trial comparing initial RRT modality among critically ill patients with severe AKI is needed to generate high-quality evidence on whether CRRT confers benefits in kidney survival and cost-effectiveness. In our study, we found that patients receiving initial therapy with CRRT not only had lower rates of dialysis dependence at 90-days, but also greater ICU and hospital-free days. These data would imply that a strategy of initial CRRT may both improve patient outcomes and be cost-effective over the short- and long-term.

This study has several strengths. It is one of the largest comparisons of CRRT and IHD to date, which afforded the ability to detect modest but clinically significant differences in outcomes between recipients of the two RRT modalities. STARRT-AKI comprised participants from 15 countries and a diversity of hospitals, thereby enabling inferences to a broad population. Data, including information on plausible confounding factors, were rigorously collected in the context of a randomized trial. Non-recovery of kidney function was defined as the ongoing receipt of RRT at 90-days. This time-point aligns with administrative definitions of end-stage kidney disease, as the ongoing receipt of dialysis at 90-days is associated with a low likelihood of subsequent kidney recovery. Moreover, the ongoing need for RRT at 90-days and the prospect of long-term maintenance dialysis is profoundly life-altering for patients and places considerable resource demands on health systems. Finally, we used several statistical methods to mitigate the risk of residual confounding to address baseline differences between patients initially treated with CRRT and IHD.

We acknowledge some limitations. While conducted using a well-curated data set from a large international RCT, this secondary analysis is subject to the same limitations inherent to all observational studies. Despite our efforts to mitigate bias, unmeasured factors, including those related to health system organization, may have resulted in treatment indication bias. CRRT recipients had better kidney function at baseline, thereby making survivors more likely to become dialysis independent at 90-days. However, overlap weighting led to good inter-group balance in baseline kidney function and all variables that we considered. We examined RRT dependence among survivors at 90-days after randomization but could not exclude further kidney recovery occurring beyond 90-days. STARRT-AKI did not mandate specific maneuvers to minimize the risk of intradialytic hypotension during IHD sessions [41], which could have biased our findings against IHD. It is possible that the association between initial RRT modality and the primary composite outcome differed in participants allocated to the accelerated RRT initiation strategy as compared to the standard strategy. This is relevant, as the results of recent randomized trials have rejected the benefits of earlier RRT initiation, and the most recent iteration of the Surviving Sepsis Clinical Practice Guidelines suggests against initiation of RRT among critically ill patients with sepsis and AKI with no definitive indications [42]. This may translate into shifts in clinical practice to a RRT initiation strategy that is more closely reflective of the standard strategy in the STARRT-AKI trial [19]. We found no significant interaction between RRT modality and the RRT initiation strategy to which patients were randomized; however, this does not definitely prove that the accelerated and standard arms behaved similarly. Finally, patients who participate in trials may be different than the broader population, which may hamper generalizability [43].

Conclusion

In this secondary analysis of the STARRT-AKI trial, the initial receipt of CRRT, as compared to IHD, was associated with a significant reduction in the risk of death or RRT dependence at 90-days, largely driven by a lower risk of RRT dependence. These observations provide new knowledge on the potential link between RRT modality and kidney recovery. While hypothesis generating, our findings should serve as a springboard for future randomized trials that can more rigorously assess the impact of RRT modality on clinical outcomes and healthcare costs.

Supplementary Information

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Abbreviations

AKI: Acute kidney injury; CKD: Chronic kidney disease; CRRT: Continuous renal replacement therapy; DM: Diabetes mellitus; GFR: Glomerular filtration rate; ICU: Intensive care unit; IHD: Intermittent hemodialysis; IPTW: Inverse probability of treatment weighting; KDIGO: Kidney Disease: Improving Global Outcomes; RRT: Renal-replacement therapy; SAPS: Simplified Acute Physiology Score; SOFA: Sequential Organ Failure Assessment.

Author details
[1] Division of Nephrology, St. Michael's Hospital, University of Toronto, Li Ka Shing Knowledge Institute, Toronto, ON, Canada. [2] AP-HP, Hôpital Avicenne, Service de Réanimation Médico-Chirurgicale, UFR SMBH, Université Sorbonne Paris Nord, Bobigny, France. [3] UMR S1155, French National Institute of Health and Medical Research (INSERM), CORAKID, Hôpital Tenon, Sorbonne Université, 75020 Paris, France. [4] Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU), Nuffield Department of Population Health, University of Oxford, Oxford, UK. [5] Department of Critical Care Medicine, Sunnybrook Health Sciences Centre and University of Toronto, Toronto, Canada. [6] Department of Intensive Care, Austin Hospital, Melbourne, Australia. [7] Department of Intensive Care, Royal Melbourne Hospital, Melbourne, Australia. [8] School of Medicine, The University of Melbourne, Melbourne, Australia. [9] Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia. [10] Department of Critical Care Medicine, Peking Union Medical College Hospital, Beijing, China. [11] The George Institute for Global Health, University of New South Wales, Kensington, NSW, Australia. [12] Intensive Care Unit, Department of Internal Medicine and Pediatrics, Ghent University Hospital, Ghent University, Ghent, Belgium. [13] Department of Medicine, Université de Sherbrooke, Centre de Recherche du CHU de Sherbrooke, Sherbrooke, QC, Canada. [14] Division of Intensive Care and Emergency Medicine, Department of Internal Medicine, Medical University Innsbruck, Innsbruck, Austria. [15] Division of Intensive Care and Nephrology, University of California San Francisco, San Francisco, CA, USA. [16] The Regional Intensive Care Unit, The Wellcome-Wolfson Institute for Experimental Medicine, Queen's University, Royal Victoria Hospital, Belfast, UK. [17] Cardiothoracic and Vascular Intensive Care Unit, Auckland City Hospital, Auckland and Medical Research Institute of New Zealand, Wellington, New Zealand. [18] Department of Critical Care Medicine, University College Dublin Clinical Research Centre at St. Vincent's University Hospital, Dublin, Ireland. [19] Monash University, Melbourne, Australia. [20] Department of Critical Care Medicine, King's College London, Guy's & St Thomas Hospital, London, UK. [21] Renal-Electrolyte Division, Department of Medicine, University of Pittsburgh, Pittsburgh, PA, USA. [22] Kidney Medicine Section, VA Pittsburgh Healthcare System, Pittsburgh, PA, USA. [23] Department of Critical Care Medicine, Zhongda Hospital Southeast University, Nanjing, China. [24] Division of Intensive Care Medicine, Department of Perioperative, Intensive Care and Pain Medicine, University of Helsinki and Helsinki University Hospital, Helsinki, Finland. [25] Department of Critical Care Medicine Centre, Hospitalier Universitaire Vaudois, Lausanne, Switzerland. [26] Department of Critical Care, Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Canada. [27] Department of Intensive Care Medicine, Department of Anesthesiology, Intensive Care and Pain Medicine, University of Helsinki and Helsinki University Hospital, Helsinki, Finland. [28] Division of Nephrology, London Health Sciences Centre, London, ON, Canada. [29] Service de Médecine Intensive Réanimation, Sorbonne Université, Hôpital Louis Mourier, Assistance Publique, Université de Paris-Cité, Paris, France. [30] Department of Critical Care Medicine, Faculty of Medicine and Dentistry, University of Alberta, and Alberta Health Services, Edmonton, AB, Canada.

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STARRT-AKI Investigators: *Steering Committee*: Sean M. Bagshaw (Co-Chair), Ron Wald (Co-Chair), Neill K. J. Adhikari, Rinaldo Bellomo, Didier Dreyfuss, Bin Du, Martin P. Gallagher, Stéphane Gaudry, Eric A. Hoste, François Lamontagne, Michael Joannidis, Kathleen D. Liu, Daniel F. McAuley, Shay P. McGuinness, Alistair D. Nichol, Marlies Ostermann, Paul M. Palevsky, Haibo Qiu, Ville Pettilä, Antoine G. Schneider, Orla M. Smith, Suvi T. Vaara, Matthew Weir. *Australia:* Austin Health: Rinaldo Bellomo, Glenn M. 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Gallagher, Rosalba Cross, Winston Cheung, Helen Wong, Mark Kol, Asim Shah, Amanda Y. 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Hoste, Stephanie Bracke, Luc De Crop, Daisy Vermeiren. *Brazil*: Hospital de Clínicas de Porto Alegre: Fernando Thome, Bianca Chiella, Lucia Fendt, Veronica Antunes. *Canada*: Centre de recherche de l'Hôpital Maisonneuve-Rosemont: Jean-Philippe Lafrance; Centre Hospitalier Universitaire de Sherbrooke: François Lamontagne, Frédérick D'Aragon, Charles St-Arnaud, Michael Mayette, Élaine Carbonnaeu, Joannie Marchand, Marie-Hélène Masse, Marilène Ladouceur; CHU de Québec-Université Laval Research Center: Alexis F. 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Whitlock, Emilie Belley-Cote, Nevena Savija, Alexandra Sabev, Troy Campbell, Thais Creary, Kelson Devereaux, Shira Brodutch; Health Sciences Centre, University of Manitoba: Claudio Rigatto, Bojan Paunovic, Owen Mooney, Anna Glybina, Oksana Harasemiw, Michelle Di Nella; Health Sciences North: John Harmon, Navdeep Mehta, Louis Lakatos, Nicole Haslam; Institut Universitaire de Cardiologie et de Pneumologie de Québec: Francois Lellouche, Mathieu Simon, Ying Tung, Patricia Lizotte, Pierre-Alexandre Bourchard; Juravinski Hospital: Bram Rochwerg, Tim Karachi, Tina Millen; Kingston Health Sciences Centre: John Muscedere, David Maslove, J. Gordon Boyd, Stephanie Sibley, John Drover, Miranda Hunt, Ilinca Georgescu; Lakeridge Health: Randy Wax, Ilan Lenga, Kavita Sridhar, Andrew Steele, Kelly Fusco, Taneera Ghate, Michael Tolibas, Holly Robinson; London Health Sciences Centre, University Hospital: Matthew A. Weir, Ravi Taneja; London Health Sciences Centre, Victoria Hospital: Ian M. Ball, Amit Garg, Eileen Campbell, Athena Ovsenek; Mazankowski Alberta Heart Institute: Sean M. Bagshaw, Sean van Diepen, Nadia Baig; McGill University Health Centre: Sheldon Magder, Han Yao, Ahsan Alam, Josie Campisi; Misericordia Community Hospital: Erika MacIntyre, Ella Rokosh, Kimberly Scherr; Mount Sinai Hospital: Stephen Lapinsky, Sangeeta Mehta, Sumesh Shah; Peter Lougheed Centre: Daniel J. Niven, Henry T. Stelfox, Stacey Ruddell; Red Deer Regional Hospital: Michael Russell, Kym Jim, Gillian Brown, Kerry Oxtoby, Adam Hall, Luc Benoit, Colleen Sokolowski; Regina Qu'Appelle Health Authority: Bhanu Prasad, Jag Rao, Shelley Giebel; Royal Alexandra Hospital: Demetrios J. Kutsogiannis, Patricia Thompson, Tayne Thompson; St. Joseph's Health Centre: Robert Cirone, Kanthi Kavikondala; St. Joseph's Healthcare: Mark Soth, France Clarke, Alyson Takaoka; St. Michael's Hospital: Ron Wald, David Mazer, Karen Burns, Jan Friedrich, David Klein, Gyan Sandhu, Marlene Santos, Imrana Khalid, Jennifer Hodder; St. Paul's Hospital: Peter Dodek, Najib Ayas, Victoria Alcuaz; Sturgeon Community Hospital: Gabriel Suen, Oleksa Rewa, Gurmeet Singh, Sean Norris, Neil Gibson, Castro Arias, Aysha Shami, Celine Pelletier; Sunnybrook Health Sciences Centre: Neill K.J. Adhikari, Alireza Zahirieh, Andre Amaral, Nicole Marinoff, Navjot Kaur, Adic Perez, Jane Wang; Surrey Memorial Hospital: Gregory Haljan, Christopher Condin; The Ottawa Hospital: Lauralyn McIntyre, Brigette Gomes, Rebecca Porteous, Irene

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Romanovsky, Oleksa Rewa, Lorena McCoshen, Nadia Baig; Vancouver Island Health Authority: Gordon Wood, Daniel Ovakim, Fiona Auld, Gayle Carney. *China*: Beijing Friendship Hospital, Capital Medical University: Meili Duan, Xiaojun Ji, Dongchen Guo, Zhili Qi, Jin Lin, Meng Zhang, Lei Dong, Jingfeng Liu, Pei Liu, Deyuan Zhi, Guoqiang Bai, Yu Qiu, Ziqi Yang, Jing Bai, Zhuang Liu, Haizhou Zhuang, Haiman Wang, Jian Li, Mengya Zhao, Xiao Zhou; Guizhou Provincial People's Hospital: Xianqing Shi, Baning Ye, Manli Liu, Jing Wu, Yongjian Fu, Dali Long, Yu Pan, Jinlong Wang, Huaxian Mei, Songsong Zhang, Mingxiang Wen, Enyu Yang, Sijie Mu, Jianquan Li, Tingting Hu; Henan Provincial People's Hospital: Bingyu Qin, Min Li, Cunzhen Wang, Xin Dong, Kaiwu Wang, Haibo Wang, Jianxu Yang; Peking Union Medical College Hospital: Bin Du, Chuanyao Wang; Peking University First Hospital: Dongxin Wang, Nan Li; Renmin Hospital of Wuhan University: Zhui Yu, Song Xu, Lan Yao, Guo Hou, Zhou Liu, Liping Lu, Yingtao Lian; Shandong Provincial Hospital: Chunting Wang, Jichen Zhang, Ruiqi Ding, Guoqing Qi, Qizhi Wang, Peng Wang, Zhaoli Meng, Man Chen, Xiaobo Hu; The First Affiliated Hospital of Bengbu Medical College: Xiandi He, Shibing Zhao, Lele Hang, Rui Li, Suhui Qin, Kun Lu, Shijuan Dun, Cheng Liu, Qi Zhou, Zhenzhen Chen, Jing Mei; The First Affiliated Hospital of Xiamen University: Minwei Zhang, Hao Xu, Jincan Lin; The First Affiliated Hospital of Xi'An Jiaotong University: Qindong Shi, Lijuan Fu, Qinjing Zeng, Hongye Ma, Jinqi Yan, Lan Gao, Hongjuan Liu, Lei Zhang, Hao Li, Xiaona He, Jingqun Fan, Litao Guo, Yu Liu, Xue Wang, Jingjing Sun; The First Hospital of Jilin University: Zhongmin Liu, Juan Yang, Lili Ding, Lulu Sheng, Xingang Liu; Wuxi People's Hospital: Jie Yan, Quihui Wang, Yifeng Wang, Dan Zhao; Xiangya Hospital Central South University: Shuangping Zhao, Chenghuan Hu, Jing Li, Fuxing Deng; Zhongda Hospital Southeast University: Haibo Qui, Yi Yang, Min Mo, Chun Pan, Changde Wu, Yingzi Huang, Lili Huang, Airan Liu. *Finland*: Helsinki University Hospital: Ville Pettilä, Suvi T. Vaara, Anna-Maija Korhonen, Sanna Törnblom, Sari Sutinen, Leena Pettilä, Jonna Heinonen, Eliria Lappi, Taria Suhonen; Tampere University Hospital: Sari Karlsson, Sanna Hoppu, Ville Jalkanen, Anne Kuitunen, Markus Levoranta, Jaakko Långsjö, Sanna Ristimäki, Kaisa Malila, Anna Wootten, Simo Varila; Turku University Hospital: Mikko J Järvisalo, Outi Inkinen, Satu Kentala, Keijo Leivo, Paivi Haltia. *France*: Hôpital Louis Mourier: Didier Dreyfuss, Jean-Damien Ricard, Jonathan Messika, Abirami Tiagarajah, Malo Emery, Aline Dechanet, Coralie Gernez, Damien Roux; Centre Hospitalier Départemental La Roche-Sur- Yon: Laurent Martin-Lefevre, Maud Fiancette, Isabelle Vinatier, Jean Claude Lacherade, Gwenhaël Colin, Christine Lebert, Marie-Ange Azais, Aihem Yehia, Caroline Pouplet, Matthieu Henry-Lagarrigue, Amélie Seguin, Laura Crosby; Medical Intensive Care Unit, Amiens University Hospital: Julien Maizel, Dimitri Titeca-Beauport; Hôpital Pitie-Salpetriere: Alain Combes, Ania Nieszkowska, Paul Masi, Alexandre Demoule, Julien Mayaux, Martin Dres, Elise Morawiec, Maxens Decalvele, Suela Demiri, Morgane Faure, Clémence Marios, Maxime Mallet, Marie Amélie Ordon, Laura Morizot, Marie Cantien, François Pousset; Hôpital Avicenne/Hôpital Jean Verdier: Stéphane Gaudry, Florent Poirson, Yves Cohen; Hospices Civils de Lyon, Hôpital Edouard Herriot, Service de Médecine Intensive – Réanimation: Laurent Argaud, Martin Cour, Laurent Bitker, Marie Simon, Romain Hernu, Thomas Baudry, Sylvie De La Salle; CH De Bourg-en-Bresse – Fleyriat: Adrien Robine, Nicholas Sedillot, Xavier Tchenio, Camille Bouisse, Sylvie Roux; CHRU de Nîmes: Saber Davide Barbar, Rémi Trusson; Rouen University Hospital: Fabienne Tamion, Steven Grangé, Dorothée Carpentier; CH Sud Francilien: Guillaume Chevrel, Luis Ensenyat-Martin, Sophie Marque; CHU Dijon: Jean-Pierre Quenot, Pascal Andreu, Auguste Dargent, Audrey Large; CH Le Mans - Réanimation Medico - Chirurgicale: Nicolas Chudeau, Mickael Landais, Benoit Derrien, Jean Christophe Callahan, Christophe Guitton, Charlène Le Moal, Alain Robert; CHU Nantes/Service d'Anesthésie - Réanimation chirurgicale HD PTMC: Karim Asehnoune, Raphaël Cinotti, Nicolas Grillot, Dominique Demeure; Germon et Gauthier Hospital – Béthune: Christophe Vinsonneau, Imen Rahmani, Mehdi Marzouk, Thibault Dekeyser, Caroline Sejourne, Mélanie Verlay, Fabienne Thevenin, Lucie Delecolle; Centre Hospitalier Lens: Didier Thevenin; Clermont Ferrand: Bertrand Souweine, Elisabeth Coupez, Mireille Adda; CH de Dieppe: Jean-Pierre Eraldi, Antoine Marchalot; Hôpital Henri Mondor: Nicolas De Prost, Armand Mekontso Dessap, Keyvan Razazi; Hôpital Civil: Ferhat Meziani, Julie Boisrame-Helms, Raphael Clere-Jehl, Xavier Delabranche, Christine Kummerlen, Hamid Merdji, Alexandra Monnier, Yannick Rabouel, Hassene Rahmani, Hayat Allam, Samir Chenaf, Vincenta Franja; CHU de Pointe à Pitre: Bertrand Pons, Michel Carles, Frédéric Martino, Régine Richard; André Mignot: Benjamin Zuber, Guillaume Lacave; CHU de Nantes: Karim Lakhal, Bertrand Rozec, Hoa Dang Van; Centre de Beaumont sur Oise: Éric Boulet; Centre Hospitalier René Dubos Pontoise: Fouad Fadel, Cedric Cleophax, Nicolas Dufour, Caroline Grant, Marie Thuong; Hotel Dieu – Service de Médicale: Jean Reignier, Emmanuel Canet, Laurent Nicolet; CHR Orleans: Thierry Boulain, Mai-Anh Nay, Dalila Benzekri, François Barbier, Anne Bretagnol, Toufik Kamel, Armelle Mathonnet, Grégoire Muller, Marie Skarzynski, Julie Rossi, Amandine Pradet, Sandra Dos Santos, Aurore Guery, Lucie Muller, Luis Felix; CH Lyon Sud – Pierre Benite: Julien Bohé, Guillaume Thiéry; Universite de Paris, Hopital Europeen Georges Pompidou: Nadia Aissaoui, Damien Vimpere, Morgane Commeureuc, Jean-Luc Diehl, Emmanuel Guerot. *Germany*: Klinikum Coburg: Orfeas Liangos, Monika Wittig; University Hospital Münster: Alexander Zarbock, Mira Küllmar, Thomas van Waegeningh, Nadine Rosenow. *Ireland*: St. Vincent's University Hospital: Alistair D. Nichol, Kathy Brickell, Peter Doran, Patrick T. Murray. *Italy*: IRCCS San Raffaele Scientific Institute: Giovanni Landoni, Rosalba Lembo, Alberto Zangrillo, Giacomo Monti, Margherita Tozzi, Matteo Marzaroli, Gaetano Lombardi; San Carlo Hospital: Gianluca Paternoster, Michelangelo Vitiello. *New Zealand*: Cardiovascular Surgical Intensive Care Unit, Auckland Hospital: Shay McGuinness, Rachael Parke, Magdalena Butler, Eileen Gilder, Keri-Anne Cowdrey, Samantha Wallace, Jane Hallion, Melissa Woolett, Philippa Neal, Karina Duffy, Stephanie Long; Department of Critical Care Medicine, Auckland Hospital: Colin McArthur, Catherine Simmonds, Yan Chen, Rachael McConnochie, Lynette Newby; Christchurch Hospital: David Knight, Seton Henderson, Jan Mehrtens, Stacey Morgan, Anna Morris, Kymbalee Vander Hayden, Tara Burke; Hawke's Bay Hospital: Matthew Bailey, Ross Freebairn, Lesley Chadwick, Penelope Park, Christine Rolls, Liz Thomas; Rotorua Hospital: Ulrike Buehner, Erin Williams; Taranaki Hospital: Jonathan Albrett, Simon Kirkham, Carolyn Jackson; Tauranga Hospital: Troy Browne, Jennifer Goodson, David Jackson, James Houghton, Owen Callender, Vicki Higson, Owen Keet, Clive Dominy; Wellington Hospital: Paul Young, Anna Hunt, Harriet Judd, Cassie Lawrence, Shaanti Olatunji, Yvonne Robertson, Charlotte Latimer-Bell, Deborah Hendry, Agnes Mckay-Vucago, Nina Beehre, Eden Lesona, Leanlove Navarra, Chelsea Robinson; Whangarei Hospital: Ryan Jang, Andrea Junge, Bridget Lambert. *Switzerland*: Centre Hospitalier Universitaire Vaudois: Antoine G. Schneider, Michel Thibault, Philippe Eckert, Sébastien Kissling, Erietta Polychronopoulos, Elettra Poli, Marco Altarelli, Madeleine Schnorf, Samia Abed Mallaird; Hôpitaux Universitaires de Genève: Claudia Heidegger, Aurelie Perret, Philippe Montillier, Frederic Sangla, Seigenthaller Neils, Aude De Watteville. *United Kingdom*: Barking, Havering and Redbridge University Hospitals NHS Trust: Mandeep-Kaur Phull, Aparna George, Nauman Hussain, Tatiana Pogreban; Barnsley Hospital NHS Foundation Trust: Steve Lobaz, Alison Daniels, Mishell Cunningham, Deborah Kerr, Alice Nicholson; Buckinghamshire Healthcare NHS Trust: Pradeep Shanmugasundaram, Judith Abrams, Katarina Manso, Geraldine Hambrook, Elizabeth McKerrow, Juvy Salva, Stephen Foulkes; Cardiff and Vale University Health Board: Matthew Wise, Matt Morgan, Jenny Brooks, Jade Cole, Tracy Michelle Davies, Helen Hill, Emma Thomas; Chelsea and Westminster Hospital NHS Foundation Trust: Marcela Vizcaychipi, Behrad Baharlo, Jaime Carungcong, Patricia Costa, Laura Martins; East Kent NHS Trust: Ritoo Kapoor, Tracy Hazelton, Angela Moon, Janine Musselwhite; Golden Jubilee National Hospital, NHS Scotland: Ben Shelley, Philip McCall; Guy's and St. Thomas' NHS Foundation Trust: Marlies Ostermann, Gill Arbane, Aneta Bociek, Martina Marotti, Rosario Lim, Sara Campos, Neus Grau Novellas, Armando Cennamo, Andrew Slack, Duncan Wyncoll, Luigi Camporota, Simon Sparkes, Rosalinde Tilley; University Hairmyres Hospital, NHS Lanarkshire: Austin Rattray, Gayle Moreland, Jane Duffy, Elizabeth McGonigal; King's College Hospital NHS Foundation Trust: Philip Hopkins, Clare Finney, John Smith, Harriet Noble, Hayley Watson, Claire-Louise Harris, Emma Clarey, Eleanor Corcoran; Leeds Teaching Hospital NHS Foundation Trust: James Beck, Clare Howcroft, Nora Youngs, Elizabeth Wilby, Bethan Ogg; Lincoln County Hospital – United Lincolnshire Hospitals NHS Foundation Trust: Adam Wolverson, Sandra Lee, Susie Butler, Maryanne Okubanjo, Julia Hindle; Liverpool University Hospitals NHS Foundation Trust: Ingeborg Welters, Karen Williams, Emily Johnson, Julie Patrick-Heselton, David Shaw, Victoria Waugh; Milton Keynes University Hospital NHS Foundation Trust: Richard Stewart, Esther Mwaura, Lynn Wren, Louise Mew, Sara-Beth Sutherland, Jane Adderley; University Hospital Monklands, NHS Lanarkshire: Jim Ruddy, Margaret Harkins; NHS Grampian: Callum Kaye, Teresa Scott, Wendy Mitchell, Felicity Anderson, Fiona Willox; North Tees and Hartlepool Foundation NHS Trust: Vijay Jagannathan, Michele Clark, Sarah Purv; Nottingham University Hospital - Queen's Medical Centre: Andrew Sharman, Megan Meredith, Lucy Ryan, Louise Conner, Cecilia Peters, Dan Harvey; Queen Elizabeth Hospital - Lewisham and Greenwich NHS Trust: Ashraf Roshdy, Amy Collins; Queen Elizabeth University

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Author contributions

RW, SG, DD and SMB conceived and designed the study in consultation with the Steering Committee. RW, SG, DD and SMB drafted the data creation plan. BRdC performed the analysis; all authors interpreted the data; RW and SMB drafted the manuscript; all authors provided substantial revisions; all authors have reviewed and approved the submitted manuscript; all authors have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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Availability of data and materials

The STARRT-AKI has a data sharing policy available at: https://www.ualberta.ca/critical-care/research/current-research/starrtaki/documents.html.

Declarations

Conflicts of Interest

SMB has received fees from Baxter for scientific advisory and speaking; fees from BioPorto for scientific advisory and clinical adjudication; fees from Novartis for scientific advisory; and fees from I-SPY-COVID for Data Safety Monitoring. RW has received unrestricted research funding and speaker fees from Baxter. RW has received consulting fees and unrestricted research funding from Baxter.

Ethical approval

The STARRT-AKI trial was approved by the research ethics boards at the University of Alberta (File # Pro00060023) and Unity Health Toronto (CTO Project ID: 0761) and 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

Not applicable.

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