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

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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.

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 1,590 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 OR, 0.90; 95% 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.

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Keywords: Acute kidney injury; renal-replacement therapy; modality; intermittent hemodialysis; continuous; mortality; randomized trial

BACKGROUND

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 ICU settings are intermittent hemodialysis (IHD) and continuous renal replacement therapy (CRRT). IHD is generally provided for 3-5 hours per session every other day, delivered with a conventional dialysis machine. Continuous renal replacement therapy (CRRT) is delivered using a specialized platform device continuously over a prolonged (>24-hour) 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.

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 3,019 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, patients allocated to the accelerated-strategy were to start RRT within 12 hours, whereas in patients allocated to the standard-strategy, clinicians were discouraged from starting RRT unless one or more conventional indications developed or if AKI persisted for >72 hours [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 hours) for critically ill 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

Patients 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 patients 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 hours of organ support or time in the ICU or hospital on that calendar day. Patients 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; 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).

RESULTS

Patients

Among 2,927 patients in the modified intention-to-treat cohort, 2,321 received RRT (1,418 allocated to the accelerated-strategy and 903 allocated to the standard-strategy). We excluded 24 patients with missing data on initial modality and 101 patients who initiated SLED. Of the remaining 2,196 (94.6%) participants, 1,590 (72.4%) initially received CRRT and 606 (27.6%) received IHD (Figure 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 patients 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%) patients who initially started IHD (unadjusted OR, 0.90; 95% CI, 0.75 to 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 to 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 composite of death or RRT dependence at 90-days was evaluated across 10 pre-specified subgroups, including the randomly allocated RRT initiation strategy (Figure 2). There were no statistically significant interactions.

Secondary outcomes

All-cause mortality at 90-days occurred in 752 (47.3%) who initially received CRRT and 279 (46.0%) who initially received IHD (unadjusted OR 1.05, 95% CI 0.87 to 1.27; OR after overlap weighting, 0.90; 95% CI, 0.74 to 1.11) (Table 2). Patients who commenced CRRT had a lower risk of RRT dependence at 90-days compared with patients who commenced IHD (unadjusted OR 0.51, 95% CI 0.35 to 0.76; OR after overlap weighting, 0.61; 95% CI, 0.39 to 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.

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 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 to 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 to 1.02) but was associated with a lower risk of RRT dependence at 90 days (0.94, 95% 0.90 to 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 patients 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 patients 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 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 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 patients 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 in order 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 baseline inter-group balance. 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 patients 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.

List of 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

Declarations

Ethics 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.

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.

Competing Interests: 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.

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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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FIGURE LEGEND

Figure 1. Assembly of the study cohort, stratified by initial receipt of CRRT or IHD

Figure 2. The association between initial RRT modality and the composite outcome of 90-day mortality or RRT dependence, across pre-specified sub-groups