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Regional Practice Variation and Outcomes in the Standard Versus Accelerated Initiation of Renal Replacement Therapy in Acute Kidney Injury (STARRT-AKI) Trial: A Post Hoc Secondary Analysis

OBJECTIVES: Among patients with severe acute kidney injury (AKI) admitted to the ICU in high-income countries, regional practice variations for fluid balance (FB) management, timing, and choice of renal replacement therapy (RRT) modality may be significant.

DESIGN: Secondary post hoc analysis of the STandard vs. Accelerated initiation of Renal Replacement Therapy in Acute Kidney Injury (STARRT-AKI) trial (ClinicalTrials.gov number NCT02568722).

SETTING: One hundred-fifty-three ICUs in 13 countries.

PATIENTS: Altogether 2693 critically ill patients with AKI, of whom 994 were North American, 1143 European, and 556 from Australia and New Zealand (ANZ).

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Total mean FB to a maximum of 14 days was +7199 mL in North America, +5641 mL in Europe, and +2211 mL in ANZ ($p < 0.001$). The median time to RRT initiation among patients allocated to the standard strategy was longest in Europe compared with North America and ANZ ($p < 0.001$; $p < 0.001$). Continuous RRT was the initial RRT modality in 60.8% of patients in North America and 56.8% of patients in Europe, compared with 96.4% of patients in ANZ ($p < 0.001$). After adjustment for predefined baseline characteristics, compared with North American and European patients, those in ANZ were more likely to survive to ICU ($p < 0.001$) and hospital discharge ($p < 0.001$) and to 90 days (for ANZ vs. Europe: risk difference [RD], −11.3%; 95% CI, −17.7% to −4.8%; $p < 0.001$ and for ANZ vs. North America: RD, −10.3%; 95% CI, −17.5% to −3.1%; $p = 0.007$).

CONCLUSIONS: Among STARRT-AKI trial centers, significant regional practice variation exists regarding FB, timing of initiation of RRT, and initial use of continuous RRT. After adjustment, such practice variation was associated with lower ICU and hospital stay and 90-day mortality among ANZ patients compared with other regions.

KEYWORDS: acute kidney injury; continuous renal replacement therapy; fluid balance; intermittent hemodialysis; outcomes; randomized controlled trial

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The management of critically ill patients with severe acute kidney injury (AKI) is complex. Furthermore, some key aspects of treatment, such as the management of fluid balance (FB), timing, and choice of initial renal replacement therapy (RRT), remain controversial and practice is variable (1–9). Prior data have shown regional variations in the characteristics of patients with AKI who are supported in ICU settings (10–12). Furthermore, clinical trials investigating the intensity of RRT have demonstrated differences in the

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KEY POINTS

Question: Are there variations in practice in the management of critically ill patients with acute kidney injury across major geographical regions (North America, Europe, and Australia and New Zealand [ANZ])?

Findings: Among 2693 patients enrolled in an international randomized controlled trial, we found significant differences in baseline patient characteristics, fluid balance, timing, and choice of first renal replacement therapy modality according to major geographic regions. After adjusting for differences in predefined baseline characteristics, ANZ patients had significantly lower 90-day mortality than those in North America and Europe.

Meaning: Significant regional variations in practice were found that may be associated with differences in patient outcomes.

practices regarding the use of intermittent RRT across regions (13, 14). Additionally, observational studies have reported significant heterogeneity in RRT practice patterns within North America (15, 16). Regarding FB management using ultrafiltration, an international survey has revealed significant practice variation (4), also regionally in North America (17) and Europe (18). Finally, surveys in the United Kingdom (19) and Australia and New Zealand (ANZ) (20) have demonstrated varying practices within nations.

The STandard vs. Accelerated initiation of Renal Replacement Therapy in Acute Kidney Injury (STARRT-AKI) trial was an international multicenter randomized controlled trial conducted in 168 centers across 15 countries. It compared two strategies of RRT initiation in patients with severe AKI who were eligible for RRT initiation but had no urgent indications for RRT initiation (7, 21, 22).

In this post hoc secondary analysis of the STARRT-AKI trial, we aimed to test the hypothesis that, among patients treated in high-income countries, there would be significant practice variation according to geographical regions in relation to: 1) FB management; 2) timing of RRT initiation among patients allocated to the standard RRT strategy; and 3) choice of initial RRT modality. We further hypothesized that such variation would be associated with differences in patient outcomes.

MATERIALS AND METHODS

Patients

STARRT-AKI enrolled 3019 critically ill adults with severe AKI (stages 2–3 using the Kidney Disease Improving Global Outcomes classification) from 168 centers in 15 countries and five continents (7) (**Fig. 1**). The trial protocol, statistical analysis plan, and the details of the main trial findings have been published (7, 21, 22). STARRT-AKI was registered at ClinicalTrials.gov (ClinicalTrials.gov Identifier: NCT02568722) and was approved by the health research ethics boards at the University of Alberta (File No. Pro00060023), Unity Health Toronto (Clinical Trials Ontario Project Identifier: 0761) and research ethics boards at all participating sites (**eTable 1**, http://links.lww.com/CCX/B310) (7). Informed consent was obtained from participants, substitute decision-makers and/or deferred or waived, as per local health research ethics board approval. The trial was conducted according to the Declaration of Helsinki and its later amendments.

Exposures

This post hoc secondary analysis aimed to evaluate regional differences in FB management, timing of RRT initiation in the standard arm, and the choice of the initial modality of RRT (Data Creation Plan available at: https://www.ualberta.ca/critical-care/media-library/documents/dcp_starrt-aki-regional-practice-variation-effect-statusv2_july-18-2022.pdf).

We pre-designated geographic regions of high-income regions: North America (Canada and United States); Europe (Austria, Belgium, Finland, France, Germany, Ireland, Italy, Switzerland, and United Kingdom), and ANZ for comparison. Patients from China (n = 255) and Brazil (n = 8) were excluded because the number of centers and patients treated in these countries was insufficient for meaningful comparisons and because both are upper middle-income countries.

Among patients with available data, we evaluated cumulative FB from the time of ICU admission over

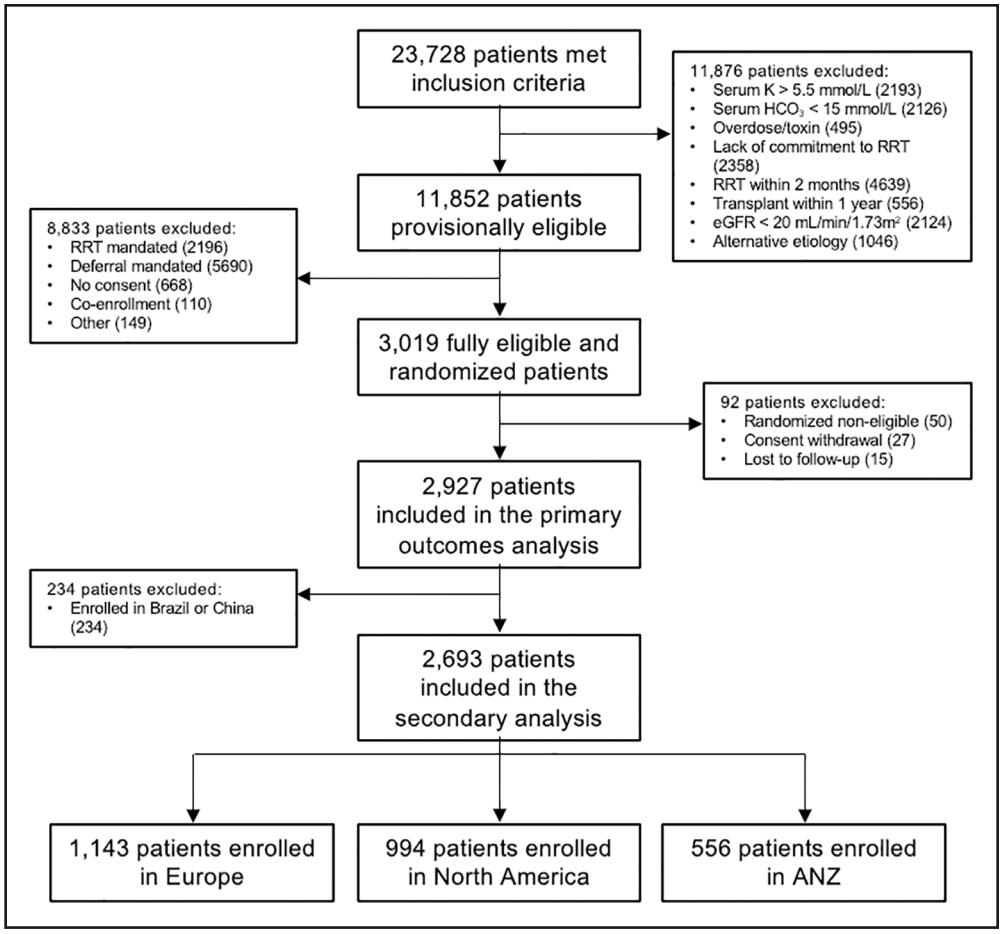

Figure 1. Study flow chart. ANZ = Australia and New Zealand, eGFR = estimated glomerular filtration rate, Hco_3 = bicarbonate, RRT = renal replacement therapy.

their entire ICU stay up to day 14 (7), the timing of initiation of RRT among those allocated to the standard strategy, and the choice of initial RRT modality according to geographic region. Patients discharged from the ICU before day 14 or who died were censored at the time of discharge or death.

Outcomes

The primary outcome was all-cause 90-day mortality. Secondary outcomes for this analysis were ICU and hospital mortality, ICU-free days at day 28, hospital-free days at day 90, and mechanical ventilation-free days at day 28. A "free day" was considered a 24-hour period in which less than 2 hours were spent in the ICU, in hospital or receiving invasive mechanical ventilation, respectively.

We also obtained kidney-specific secondary outcomes, including RRT dependence at day 90, the composite of mortality and persistent use of RRT at 90 days, and RRT-free days at day 90.

Sensitivity Analyses

As patient management may be different in medical and surgical patients, especially regarding FB, we performed several sensitivity analyses: 1) among medical patients only, 2) excluding cardiac surgical patients, and 3) excluding all elective surgical patients. Additionally, we performed separate comparisons according to the allocated RRT initiation strategy. Finally, we analyzed geographic regions by dividing Europe into French and non-French European centers. This subdivision was based on the premises that these jurisdictions have differing healthcare systems, have traditionally shown differences in approach to RRT, and had sufficient sample size to enable meaningful comparison (3, 8).

Statistical Analyses

We applied the intention-to-treat approach as used in the primary trial analysis. Continuous variables are reported as median (quartile 25th–quartile 75th) and compared using the Wilcoxon rank-sum or Kruskal-Wallis test. Categorical variables are reported using absolute numbers (percentage) and compared using Fisher exact test.

Binary outcomes were compared between groups using risk difference (and 95% CI) calculated with a generalized linear model with a binomial distribution and identity link. We used the risk difference for description of varying practices and associated outcomes to minimize attribution of judgment when directly comparing geographic regions. Continuous outcomes were compared between groups using median difference (and 95% CI) calculated with a median

regression using an interior point algorithm with CI and p values calculated after bootstrapping with 1000 samples. Bootstrap was used to construct robust SEs as described elsewhere (23). In addition to univariable models, multivariable models were performed after adjustment for prespecified covariates, including age, sex, Simplified Acute Physiology Score (SAPS) II score, type of admission (surgical vs. medical), and presence of sepsis. These covariates were chosen because they aligned with the main STARRT-AKI statistical analysis plan (7, 21, 22). The study site was also included as a random effect. The supplement provides **Additional Methods** (http://links.lww.com/CCX/B310) about non-normally distributed data and about variable selection for sensitivity analyses. Finally, 90-day survival was reported in Kaplan-Meier curves and compared between groups using the log-rank test.

All analyses were performed using R (Version 4; R Project for Statistical Computing, Vienna, Austria. Available at: https://www.r-project.org/). Given multiple comparisons, the significance level was adjusted with the Bonferroni method. A p value of less than 0.01 was considered statistically significant.

RESULTS

Patient Characteristics According to Geographic Region

We included 2927 patients with complete data after randomization in this analysis. After exclusion of patients enrolled in China and Brazil, we analyzed 994 patients enrolled in North America, 1143 in Europe, and 556 in ANZ (**Table 1** and Fig. 1).

There were multiple regional differences in baseline patient characteristics, risk factors for AKI, and pre-randomization management (Table 1; and **eTable 2**, http://links.lww.com/CCX/B310). For example, European patients were the oldest and most likely to be admitted with a medical condition. Patients from ANZ were more likely to be admitted after surgery and with a primary cardiovascular admission diagnosis. Sepsis was the primary ICU admission diagnosis in 25.6% of patients from North America and Europe. Patients from ANZ had the highest exposure to cardiopulmonary bypass and IV contrast media (eTable 2, http://links.lww.com/CCX/B310). North American patients had the largest proportion receiving mechanical ventilation, whereas ANZ had the largest proportion receiving norepinephrine and diuretics (Table 1).

Fluid Balance According to Geographic Region

Before randomization, the cumulative FB was highest among North American patients, with almost twice the value of European and ANZ patients, respectively (Table 1). Additionally, the cumulative FB from randomization or ICU admission was significantly more positive in North American and European patients than in ANZ patients (**Table 2** and **Fig. 2**). When medical and surgical patients were analyzed separately, the result remained the same (**eTable 3**, http://links.lww.com/CCX/B310). **eFigure 1** (http://links.lww.com/CCX/B310) presents the FB according to quintiles of SAPS II score in different regions and shows that ANZ patients had less positive FB than patients in other regions regardless of the severity of illness.

Timing and Choice of Initial RRT Modality

In the standard strategy, time to RRT varied from a median of 30.7 hours in North America to 27.5 hours in ANZ and 48.0 hours in Europe ($p < 0.001$) (Table 1). In the accelerated strategy, the timing of initiation of RRT was clinically similar across regions.

Intermittent hemodialysis (IHD) was the initial RRT modality in 41.7% of European and 30.1% of North American patients, compared with only 0.7% of ANZ patients (Table 1). The initial use of continuous RRT (CRRT) was essentially the inverse. Use of sustained low-efficiency daily dialysis was infrequent and primarily confined to North America.

Unadjusted Patient Outcomes According to Geographic Regions

There were significant differences in unadjusted 90-day mortality among regions (**Table 3**). In ANZ centers, ICU and hospital mortality were lower, and ICU, hospital, RRT, and ventilator-free days were greater compared with North American and European sites, respectively. Additionally, ANZ patients had the lowest proportion of dependence on RRT at 90 days and fewer patients with the combined outcome of death or RRT dependence at day 90 (Table 3). These observations were consistent when the cohort was stratified by allocation to accelerated or standard

TABLE 1.
Baseline Characteristics

Characteristic	North America ($n = 994$)	Europe ($n = 1143$)	Australia and New Zealand ($n = 556$)	p
Age, yr	65.4 (56.7–73.5)	68.4 (58.9–76.0)	66.7 (56.6–75.0)	< 0.001
Male gender	672 (67.6)	795 (69.6)	367 (66.0)	0.293
Weight, kg	89.0 (73.6–108.0)	82.0 (70.5–95.0)	87.0 (73.6–102.4)	< 0.001
Simplified Acute Physiology Score II	62.0 (50.0–74.0)	55.0 (44.0–69.0)	61.0 (47.0–74.2)	< 0.001
Randomization group				0.997
Accelerated arm	497 (50.0)	572 (50.0)	277 (49.8)	
Standard arm	497 (50.0)	571 (50.0)	279 (50.2)	
Hours between randomization and renal replacement therapy	7.5 (4.2–26.0)	12.1 (8.7–32.3)	22.6 (19.3–36.8)	< 0.001
Accelerated arm	5.1 (3.2–7.0)	9.3 (7.9–11.8)	6.3 (4.2–9.0)	< 0.001
Standard arm	28.9 (21.0–58.9)	52.5 (29.8–84.0)	40.9 (31.1–63.3)	< 0.001
Initial modality				< 0.001
Continuous renal replacement therapy	481 (60.8)	492 (56.8)	422 (95.7)	
Intermittent hemodialysis	238 (30.1)	361 (41.7)	3 (0.7)	
Sustained low-efficiency daily dialysis	72 (9.1)	13 (1.5)	16 (3.6)	
Type of admission				< 0.001
Medical	686 (69.0)	854 (74.7)	267 (48.0)	
Scheduled surgery	114 (11.5)	108 (9.4)	116 (20.9)	
Unscheduled surgery	194 (19.5)	181 (15.8)	173 (31.1)	
Pre-randomization clinical frailty score	3.0 (2.0–4.0)	2.0 (0.0–4.0)	3.0 (1.0–4.0)	< 0.001
Pre-randomization signs				
Respiratory rate, breaths/min	24.0 (18.0–29.0)	23.0 (18.0–29.0)	20.0 (16.0–24.0)	< 0.001
Positive end-expiratory pressure, cm H_2O	10.0 (8.0–12.0)	8.0 (5.0–10.0)	8.0 (6.0–10.0)	< 0.001
Cumulative fluid balance, mL	4267 (1777–8827)	2400 (750–4650)	2103 (626–4405)	< 0.001
Pre-randomization blood tests				
pH	7.32 (7.26–7.38)	7.34 (7.27–7.39)	7.33 (7.26–7.39)	0.019
Creatinine, μmol/L	295.0 (226.0–399.0)	265.6 (202.0–359.0)	260.0 (208.5–356.5)	< 0.001
Hemoglobin, g/L	90.0 (79.0–106.0)	102.0 (86.0–118.0)	96.0 (83.0–116.0)	< 0.001
Platelets, $\times 10^9$/L	140.0 (78.0–217.0)	166.0 (96.0–250.0)	148.0 (90.8–218.2)	< 0.001
Pre-randomization support				
Mechanical ventilation or continuous positive airway pressure	807 (88.9)	864 (75.6)	440 (79.1)	< 0.001
Norepinephrine use	645 (64.9)	726 (63.5)	410 (73.7)	< 0.001
Norepinephrine dose, μg/kg/min	0.2 (0.1–0.3)	0.3 (0.1–0.7)	0.2 (0.1–0.3)	< 0.001
Diuretic use	340 (34.2)	289 (25.3)	233 (41.9)	< 0.001

Data are median (quartile 25th–quartile 75th) or *n* (%).

TABLE 2.
Fluid Balance to a Maximum of 14 ICU Days From Randomization and From ICU Admissions Across Geographic Regions

Variable	North America (*n* = 994)	Europe (*n* = 1,143)	Australia and New Zealand (*n* = 556)	*p*
Fluid balance, mL				
Mean daily	283.9 (−342.1 to 1,158.5)	436.7 (−224.3 to 1,302.8)	−56.8 (−537.0 to 548.8)	< 0.001
Median daily	263.0 (−365.0 to 1,036.0)	432.5 (−235.0 to 1,299.0)	61.8 (−444.9 to 556.4)	< 0.001
Total	2,018.0 (−2,731.5 to 9,007.5)	2,900.0 (−1,932.5 to 9,179.0)	−493.0 (−4,342.2 to 3,458.0)	< 0.001
Fluid balance[a], mL				
Mean daily	788.5 (94.9 to 1,790.6)	668.8 (28.9 to 1,597.4)	266.2 (−181.1 to 795.5)	< 0.001
Median daily	400.0 (−204.6 to 1,236.5)	548.8 (−80.0 to 1,365.4)	138.2 (−259.2 to 656.1)	< 0.001
Total	7,199.0 (700.5 to 16,129.5)	5,641.0 (157.0 to 13,713.5)	2,211.5 (−1,857.8 to 6,638.2)	< 0.001

[a]Including pre-randomization fluid balance.
Data are median (quartile 25th–quartile 75th) or *n* (%).

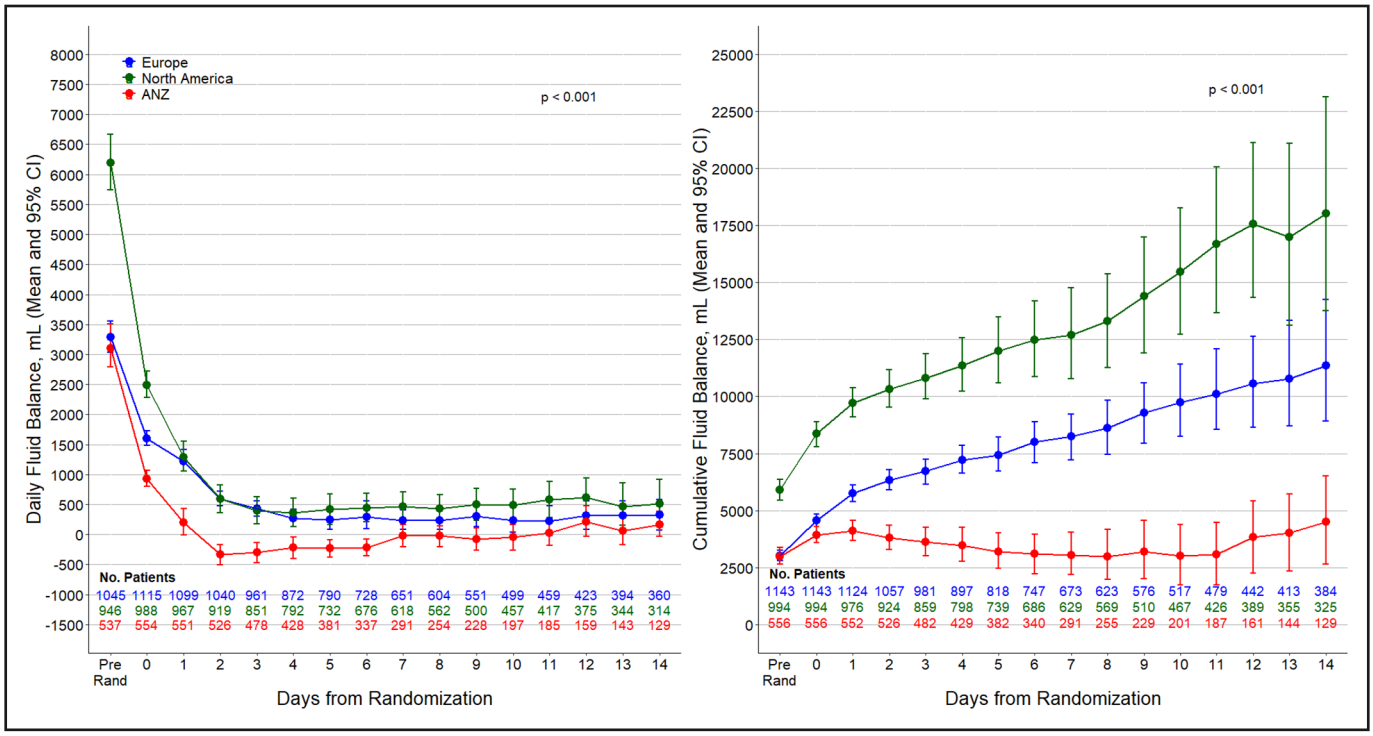

Figure 2. Daily and cumulative fluid balance according to geographical regions. ANZ = Australia and New Zealand.

RRT initiation (**eFigs. 2** and **3**, http://links.lww.com/CCX/B310).

Adjusted Patient Outcomes According to Geographic Regions

On univariable analysis, the differences between North America and Europe were confined to RRT-free days at 90 days, which were significantly higher in European patients. Compared with North America and Europe, ANZ patients experienced more favorable outcomes across all measures (**eTable 4**, http://links.lww.com/CCX/B310).

In the multivariable model, adjusted for age, sex, SAPS II score, admission type, and sepsis, there were no differences in outcomes between North America and

TABLE 3.
Unadjusted Clinical Outcomes Stratified by Geographic Region

Outcome	North America (*n* = 994)	Europe (*n* = 1143)	Australia and New Zealand (*n* = 556)	*p*
90-d mortality	456/994 (45.9)	514/1143 (45.0)	177/556 (31.8)	< 0.001
Hospital outcomes				
ICU mortality	364/994 (36.6)	389/1143 (34.0)	125/556 (22.5)	< 0.001
Hospital mortality	421/994 (42.4)	461/1142 (40.4)	154/549 (28.1)	< 0.001
ICU-free days at day 28	3.5 (0.0–19.0)	4.0 (0.0–20.0)	16.0 (0.0–22.0)	< 0.001
Hospital-free days at day 90	0.0 (0.0–60.8)	4.0 (0.0–62.0)	50.0 (0.0–71.0)	< 0.001
Ventilator-free days at day 28	9.0 (0.0–22.0)	10.0 (0.0–24.0)	20.0 (0.0–25.0)	< 0.001
Renal outcomes				
RRT dependence at day 90	55/529 (10.4)	49/622 (7.9)	12/379 (3.2)	< 0.001
Death or RRT dependence at day 90	511/985 (51.9)	563/1136 (49.6)	189/556 (34.0)	
RRT-free days at day 90	8.5 (0.0–85.0)	59.0 (0.0–89.0)	82.0 (0.0–88.0)	< 0.001
Death category				0.011
Cardiovascular	288/455 (63.3)	282/510 (55.3)	116/172 (67.4)	
Metabolic	60/455 (13.2)	65/510 (12.7)	18/172 (10.5)	
Neurologic	18/455 (4.0)	35/510 (6.9)	12/172 (7.0)	
Respiratory	89/455 (19.6)	128/510 (25.1)	26/172 (15.1)	

RRT = renal replacement therapy.
Data are median (quartile 25th–quartile 75th) or *n* (%).

Europe (**Table 4**). In contrast, there remained significant differences between patients in ANZ, who had better outcomes, compared with North America. The same pattern was observed when ANZ patients were compared with European patients, except there was no difference in RRT dependence at day 90. Additional analyses after adjustment for multiple statistically imbalanced baseline variables, including cumulative FB at randomization are reported in **eTable 5** (http://links.lww.com/CCX/B310).

Sensitivity Analyses

In sensitivity analysis among medical patients only, the key outcomes were aligned with those of the main analysis (**eTables 6** and **7**, http://links.lww.com/CCX/B310). Furthermore, findings were similar in analyses excluding the cardiac surgical patients (**eTables 8** and **9**, http://links.lww.com/CCX/B310) and after excluding all elective surgical patients (**eTables 10** and **11**, http://links.lww.com/CCX/B310).

Additional analyses according to allocation to the accelerated and standard strategy arms replicated the patterns seen in the entire cohorts (**eTables 12** and **13**, http://links.lww.com/CCX/B310).

Finally, we found French patients commenced IHD more frequently than other European patients (**eTable 14**, http://links.lww.com/CCX/B310) and had a significantly more positive FB than non-French European patients (**eTable 15**, http://links.lww.com/CCX/B310). Additionally, we found no significant outcome differences for French vs. non-French European patients when a clinical model was applied (**eTable 16**, http://links.lww.com/CCX/B310). In an alternative statistically derived model, however, differences in mortality in ICU, hospital, and 90 days, along with ventilator-free, ICU-free, and hospital-free days were evident (**eTable 17**, http://links.lww.com/CCX/B310).

DISCUSSION

Key Findings

In a post hoc secondary analysis of the STARRT-AKI trial, we found significant differences in patient

TABLE 4.
Multivariable Models for Key Outcomes

Outcome	North America vs. Europe		ANZ vs. Europe		ANZ vs. North America	
	Effect Estimate (95% CI)	*p*	Effect Estimate (95% CI)	*p*	Effect Estimate (95% CI)	*p*
90-d mortality (RD)	−0.37 (−6.32 to 5.60)	0.904	−11.31 (−17.74 to −4.85)	0.001	−10.27 (−17.47 to −3.07)	0.007
ICU mortality (RD)	−0.18 (−5.61 to 5.26)	0.949	−11.63 (−17.69 to −5.57)	< 0.001	−11.66 (−18.02 to −5.29)	0.001
Hospital mortality (RD)	0.39 (−5.25 to 6.05)	0.892	−10.96 (−16.95 to −4.97)	0.001	−10.98 (−17.92 to −4.06)	0.003
RRT dependence at day 90 (RD)	2.81 (−1.76 to 7.39)	0.234	−4.61 (−9.72 to 0.52)	0.083	−7.85 (−11.38 to −4.31)	< 0.001
Death or RRT dependence at day 90 (RD)	−0.34 (−6.36 to 5.69)	0.911	−11.56 (−18.10 to −4.99)	0.001	−10.50 (−17.74 to −3.24)	0.006
ICU-free days at day 28 (MD)	0.51 (−1.40 to 2.43)	0.599	5.86 (3.40–8.33)	< 0.001	4.72 (1.82–7.63)	0.001
Hospital-free days at day 90 (MD)	−0.59 (−6.54 to 5.36)	0.846	18.38 (9.74–27.03)	< 0.001	17.27 (7.12–27.43)	0.001
Ventilator-free days at day 28 (MD)	0.31 (−2.28 to 2.91)	0.812	6.27 (3.41–9.14)	< 0.001	5.72 (2.53–8.91)	< 0.001
RRT-free days at day 90 (MD)	−5.03 (−15.41 to 5.35)	0.342	18.74 (5.94–31.53)	0.004	25.67 (8.94–42.41)	0.003

ANZ = Australia and New Zealand, MD = median difference, RD = risk difference, RRT = renal replacement therapy.

RD calculated from a multivariable generalized linear model with binomial distribution and identity link.

MD calculated from a multivariable median regression using an interior point algorithm.

All models adjusted for age, sex, Simplified Acute Physiology Score II, type of admission (surgical vs. medical), and presence of sepsis. Sites were entered as random effect.

characteristics, management, and RRT provision across three major geographic regions. Patients treated in North American and European centers had a more positive FB and were more likely to receive IHD as the initial modality of RRT, compared with those treated in ANZ centers. After adjusting for differences in predefined baseline characteristics, ANZ patients had better outcomes than those in North America and Europe, including a significantly lower 90-day mortality. The results of sensitivity analyses of the subgroup of medical patients, and subgroups excluding cardiac surgical and elective surgical patients aligned with those of the main analysis. However, there remained further variation within these geographic regions, likely due to aspects of both ICU and RRT organization (e.g., case-mix, ICU organization, staffing models, multidisciplinary teams) that differ between countries. For example, adverse patient outcomes have been associated with higher patient-to-nurse ratios, including adverse events, length of stay, and risk-adjusted mortality (24, 25). The availability of ICU beds and trained critical care personnel has also been associated with patient outcomes (26).

Relationship to Previous Studies

Regional variations in the baseline characteristics of patients with AKI in general and those admitted to the ICU and either treated with RRT or characterized by stage 2 or 3 AKI have been reported for over 2 decades (10–12). These differences likely reflect regional differences in population health and disease characteristics, regional variation in ICU admission criteria, utilization and resources, and differences in the access to and organization of ICU services. Our findings expand such previous observations. Furthermore, regional differences have been reported for other aspects of critical care, including ventilation mode (27, 28) and the use of vasopressors and fluid resuscitation in septic patients (29).

The potential adverse consequences of fluid accumulation in critically ill patients in general, in patients receiving RRT, or those with severe AKI have been described (30–33). In aggregate, these studies have shown a less positive FB among patients treated with CRRT and those treated in ANZ compared with North America (13, 14). We reported consistently lower daily cumulative FB among both medical and surgical patients treated in ANZ compared with European or North American patients, extending previous observations about regional fluid management practices. Of note, another secondary analysis of the STARRT-AKI trial found that accelerated RRT initiation did not confer benefit in 90-day mortality among those with marked fluid accumulation compared with standard strategy, emphasizing that regional practices for fluid administration may be a more important determinant of fluid accumulation (34).

Regional variation in the timing and choice of initial RRT modality and the duration of its application have been characterized (35–38) and recently highlighted by a comparison of data from the two key randomized trials of RRT intensity (13, 14). The findings of our study confirm and extend the observation that there is a preferential use of CRRT as the modality of first choice in ANZ compared with an approach that combines IHD and CRRT in North America and Europe. Recently, another post hoc secondary analysis of the STARRT-AKI trial confirmed that initial use of CRRT, compared with IHD, was associated with a reduction in the composite outcome of death or dialysis dependence at 90 days (39).

A unique feature of this secondary analysis compared with previous comparative studies is that all patients were recruited and randomized within the same randomized trial using the same eligibility criteria. Thus, their baseline characteristics before randomization were documented in detail, and evaluation of the association between world regions and outcomes could be adjusted for baseline characteristics. Significant regional differences in practice and outcomes remained, after adjustment for baseline features, which is an important finding in the setting of a large international RCT where the standard-strategy arm was not strictly protocolized.

Implications of Study Findings

Our study found that within the context of the STARRT-AKI trial, there were major regional variations in the characteristics of critically ill patients considered for RRT. Furthermore, such differences were associated with differences in achieved FB during the first 2 weeks of management in the ICU and the timing and choice of the initial modality of RRT. Finally, after adjustment and within the limitations of the available data, our

analysis suggests that FB and RRT practice styles may be associated with outcomes. These findings should be considered when designing future trials investigating fluid management and RRT related aspects.

Study Strengths and Limitations

This study has several strengths. First, the data were obtained from the largest randomized study of RRT in ICU conducted to date. Such broad representation from centers worldwide bolsters the generalizability of our findings. Second, data were rigorously collected and reviewed using explicit criteria. Baseline characteristics were collected in detail, thus minimizing ascertainment bias. Third, randomization was concealed, minimizing selection bias. Fourth, all patients' inclusion criteria were standardized, minimizing indication bias. Finally, follow-up was rigorous and independent of treatment allocation or choice of RRT modality or FB achieved, thus minimizing performance bias.

We acknowledge several limitations. This post hoc observational analysis of data from a randomized trial is susceptible to the known limitations of such studies, including the inability to draw inferences about causation. First, the geographic regions selected were arbitrary and based on simple geographic proximity. We recognize there is likely significant variation between specific countries (3, 8, 13, 14), between centers in countries and even within individual centers; however, our objective with this secondary analysis was to provide a high-level description of practice variation within the context of a large international randomized trial. Furthermore, we recognize that enrollment contributions between countries (and centers) were from a broad diversity of hospitals and were also variable. This may limit inferences in circumstances where countries were represented by few centers enrolling many patients or vice versa. Second, we only captured data on FB in the trial through the first 14 days (34). Further, while we recorded data on FB at trial randomization and follow-up, we did not collect information on additional factors that may have influenced FB, notably the nature of fluid intake and output and the use of diuretics. Furthermore, FB does not reflect intravascular volume status and may not accurately reflect organ edema. In an observational study like ours, the association between a particular regional style of practice (less positive FB and greater use of CRRT) with better outcomes is only hypothesis-generating. Furthermore, the study centers from a given region may not necessarily reflect similar patient case-mix (i.e., sepsis, post-surgical) or management styles in all or even most ICUs in that region and selected regions are represented by variable sample sizes in our analysis. Yet, the clinical importance of the differences observed by regions both support the concept that regional practice variation is real and associates with patient outcomes. In our study, adjustments were made for key predefined baseline characteristics; however, many residual unmeasured confounders likely remain, which may impact our findings. The outcomes and FB may be driven by differences in patient characteristics and variables not recorded at baseline in the study. Such factors could plausibly include differences in how critical care is organized and provided across regions (e.g., variation in nurse-to-patient ratios). Furthermore, we only assessed the choice of initial RRT modality and could not describe the complexity of subsequent management. In this regard, shifts in FB and transitions in RRT modality reflect changes in patients' conditions and medical responses thereto, such that FB and RRT modality may be markers, rather than drivers, of patient outcomes.

CONCLUSIONS

In a post hoc secondary analysis of a large international randomized trial comparing accelerated vs. standard RRT initiation in critically ill patients with AKI, we observed differences in the crude and severity of illness adjusted outcomes and management styles across geographical regions regarding FB, initial RRT modality, and in the standard-strategy arm of the trial, the time to starting RRT. Considering these findings, this hypothesis-generating study provides the rationale and justification for randomized controlled trials that assess the impact of a less positive FB using a CRRT-predominant approach.

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Dr. Vaara, Dr. Serpa Neto, Dr. Bellomo, Wald, Dr. Bagshaw, and Dr. Ostermann were involved in study concept and design. Drs. Vaara and Bagshaw drafted the article. Dr. Serpa Neto conducted the statistical analysis. All authors were involved in acquisition of data and interpretation of results. All authors were involved in critical revision of the article for important intellectual content.

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STandard vs. Accelerated initiation of Renal Replacement Therapy in Acute Kidney Injury (STARRT-AKI) investigators listed in the online supplement (page 28) (and available at: https://www.ualberta.ca/critical-care/research/current-research/starrtaki/documents.html).

All members of the writing committee agreed to publication of this article.

The STandard vs. Accelerated initiation of Renal Replacement Therapy in Acute Kidney Injury trial (STARRT-AKI) data sharing statement will generally align with the data sharing policy of The George Institute for Global Health (https://www.georgeinstitute.org/data-sharing-policy). The STARRT-AKI Co-Chairs and Steering Committee support the view that research data generated from publicly funded research should be made available for sharing to enhance public well-being, to maximize the potential knowledge gained, to reduce redundant research, and to facilitate scientific discovery and innovation. Data sharing will be for the purposes of medical research and under the auspices of the consent under which the data were originally gathered. De-identified individual participant data collected during the STARRT-AKI trial will be shared beginning 2 years after the publication of the primary and secondary analyses, with no end date. Data will be made available to qualified researchers who provide a detailed and methodologically sound proposal with specific aims that are clearly outlined. To gain access, qualified researchers will need to sign a data sharing and access agreement and will need to

confirm that data will only be used for the purpose for which data access was granted. Proposals should be directed to the trial Co-Chairs via email: bagshaw@ualberta.ca and Ron.Wald@unityhealth.to.

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