Timing of Initiation of Renal-Replacement Therapy in Acute Kidney Injury

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ABSTRACT

BACKGROUND

Acute kidney injury is common in critically ill patients, many of whom receive renal-replacement therapy. However, the most effective timing for the initiation of such therapy remains uncertain.

METHODS

We conducted a multinational, randomized, controlled trial involving critically ill patients with severe acute kidney injury. Patients were randomly assigned to receive an accelerated strategy of renal-replacement therapy (in which therapy was initiated within 12 hours after the patient had met eligibility criteria) or a standard strategy (in which renal-replacement therapy was discouraged unless conventional indications developed or acute kidney injury persisted for >72 hours). The primary outcome was death from any cause at 90 days.

RESULTS

Of the 3019 patients who had undergone randomization, 2927 (97.0%) were included in the modified intention-to-treat analysis (1465 in the accelerated-strategy group and 1462 in the standard-strategy group). Of these patients, renal-replacement therapy was performed in 1418 (96.8%) in the accelerated-strategy group and in 903 (61.8%) in the standard-strategy group. At 90 days, death had occurred in 643 patients (43.9%) in the accelerated-strategy group and in 639 (43.7%) in the standard-strategy group (relative risk, 1.00; 95% confidence interval [CI], 0.93 to 1.09; P=0.92). Among survivors at 90 days, continued dependence on renal-replacement therapy was confirmed in 85 of 814 patients (10.4%) in the accelerated-strategy group and in 49 of 815 patients (6.0%) in the standard-strategy group (relative risk, 1.74; 95% CI, 1.24 to 2.43). Adverse events occurred in 346 of 1503 patients (23.0%) in the accelerated-strategy group and in 245 of 1489 patients (16.5%) in the standard-strategy group (P<0.001).

CONCLUSIONS

Among critically ill patients with acute kidney injury, an accelerated renal-replacement strategy was not associated with a lower risk of death at 90 days than a standard strategy. (Funded by the Canadian Institutes of Health Research and others; STARRT-AKI ClinicalTrials.gov number, NCT02568722.)

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This article was updated on July 16, 2020, at NEJM.org.

ACUTE KIDNEY INJURY IS A COMMON complication in patients admitted to an intensive care unit (ICU) and is associated with a high risk of death or major complications and a high level of resource use.[1] Many patients who are seriously ill undergo renal-replacement therapy; however, the appropriate timing for the initiation of such therapy remains uncertain. When acute kidney injury is complicated by major metabolic disorders (e.g., acidosis, hyperkalemia, and uremia) and fluid disturbances that can be treated with renal-replacement therapy, there is general consensus that such therapy should be initiated.[2,3] However, when severe acute kidney injury is not accompanied by one of these complications, the benefits of renal-replacement therapy are unclear.[4-9]

The initiation of renal-replacement therapy before the onset of major complications has conceivable advantages for patients with severe acute kidney injury. Such therapy can restore and maintain acid–base homeostasis, mitigate fluid accumulation, and reduce exposure to the metabolic hazards of untreated acute kidney injury.[10] However, wide adoption of early renal-replacement therapy in these patients may lead to initiation in those who would have survived and recovered kidney function without such therapy.[5] Furthermore, given the risks of renal-replacement therapy, establishing whether earlier initiation can improve outcomes is important for patient care. Randomized trials that have compared early and delayed strategies for starting renal-replacement therapy in critically ill patients with acute kidney injury have shown discrepant findings.[4-7]

Here, we report the results of a multinational, randomized, open-label, controlled trial (STARRT-AKI [Standard versus Accelerated Initiation of Renal-Replacement Therapy in Acute Kidney Injury]) to compare the effect of two strategies (accelerated initiation vs. standard initiation) in critically ill patients with acute kidney injury. We hypothesized that an accelerated strategy for renal-replacement therapy would result in a lower risk of death from any cause at 90 days than a standard strategy.

METHODS

TRIAL DESIGN AND OVERSIGHT

We conducted STARRT-AKI at 168 hospitals in 15 countries. A complete list of participating

sites is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org. The protocol along with its statistical analysis plan (also available at NEJM.org) was published previously.[11,12] The investigators designed the trial, wrote the manuscript, and vouch for the accuracy and completeness of the data and the analyses, for the adherence of the trial to the protocol, and for the complete reporting of adverse events. The funding organizations and partners were not involved in the design, implementation, or management of the trial, in the analysis of the data, or in the decision to submit the manuscript for publication.

Approval for the conduct of the trial was obtained from the institutional review board at each participating site. We obtained written informed consent from patients or substitute decision makers unless the requirement for informed consent was waived, according to local standards and legislation. An independent data and safety monitoring board provided trial oversight. Interim analyses to evaluate the primary outcome were performed when enrollment reached 25%, 50%, and 75% of the target (Table S1 in the Supplementary Appendix).

SELECTION OF PATIENTS

Patients were eligible if they were 18 years or older and had been admitted to an ICU with kidney dysfunction (serum creatinine level, ≥1.13 mg per deciliter [100 μmol per liter] in women and ≥1.47 mg per deciliter [130 μmol per liter] in men) and severe acute kidney injury that was categorized as stage 2 or 3 of the Kidney Disease: Improving Global Outcomes (KDIGO) classification (in which stages range from 1 to 3, with higher stages indicating greater severity). This determination of kidney injury was defined by a doubling of the serum creatinine level from baseline, a serum creatinine level of 4 mg per deciliter (354 μmol per liter) or more with an increase of 0.3 mg per deciliter (27 μmol per liter) from baseline, or a urine output of less than 6 ml per kilogram of body weight during the preceding 12 hours. The exclusion criteria were focused on emergency indications, previous renal-replacement therapy, advanced chronic kidney disease, and uncommon causes of acute kidney injury (as detailed in Table S2). The presence of all the inclusion criteria and none of the first eight exclusion criteria established provisional eligibility (Fig. S1).

To confirm full eligibility, patients' attending physicians were asked to affirm clinical equipoise by noting the absence of any circumstances that would mandate either immediate initiation of renal-replacement therapy or a deferral of such therapy because of clinical judgment regarding the likelihood of imminent recovery of kidney function. After a determination of full eligibility, a 12-hour window was allotted for consent (as applicable), randomization, and the initiation of renal-replacement therapy for patients in the accelerated-therapy group.

At baseline, we evaluated patients using the Simplified Acute Physiology Score (SAPS) II on a scale that ranges from 0 to 163, with higher scores indicating more severe disease and a higher risk of death. Patients were also evaluated with the Sequential Organ Failure Assessment (SOFA) on a scale that ranges from 0 to 24, with higher scores indicating more severe disease and a higher risk of death.

RANDOMIZATION AND INTERVENTIONS

Patients were randomly assigned in a 1:1 ratio to receive a strategy of accelerated or standard initiation of renal-replacement therapy. Randomization with variable block size (2 and 4) and site stratification were implemented with the use of a centralized Web-based platform.

In the accelerated-strategy group, clinicians were to start renal-replacement therapy as soon as possible and within 12 hours after patients had met full eligibility criteria. In the standard-strategy group, clinicians were discouraged from initiating renal-replacement therapy until the development of one or more of the following criteria: a serum potassium level of 6.0 mmol or more per liter, a pH of 7.20 or less or a serum bicarbonate level of 12 mmol per liter or less, evidence of severe respiratory failure based on a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen of 200 or less and clinical perception of volume overload, or persistent acute kidney injury for at least 72 hours after randomization. For patients in the standard-strategy group, clinicians were not obligated to initiate renal-replacement therapy. Similarly, clinicians had discretion to initiate such therapy at any time if they perceived that deferral was no longer in the patient's best interest.

The protocol provided recommendations for the delivery of renal-replacement therapy that aligned with recognized international guidelines.[13] Discontinuation of renal-replacement therapy occurred at the time of recovery of kidney function, withdrawal of life-sustaining support, or death.

OUTCOMES

The primary outcome was death from any cause at 90 days after randomization. Key secondary outcomes at 90 days were dependence on renal-replacement therapy; a composite of death or dependence on renal-replacement therapy; and a major adverse kidney event, which was defined as death, dependence on renal-replacement therapy, or a sustained reduction in kidney function (i.e., an estimated glomerular filtration rate [eGFR] of <75% of the baseline value[14]). Additional prespecified secondary outcomes included death in the ICU at 28 days or during hospitalization; the number of days free of renal-replacement therapy at 90 days; the number of ventilator-free and vasoactive-free days at 28 days[4,15]; the length of hospitalization and hospitalization-free days at 90 days; and health-related quality-of-life, as assessed at 90 days by means of the European Quality of Life–5-Dimensions 5-Level questionnaire (EQ-5D-5L; scores range from 0 to 100, with higher scores indicating a better quality of life).[16]

Adverse events related to renal-replacement therapy and vascular access were reported through 14 days among all the patients who had undergone randomization and remained in the ICU. All serious adverse events were reviewed by the cochairs of the trial and by the chair of the data and safety monitoring board within 48 hours after notification.

STATISTICAL ANALYSIS

We performed all analyses in accordance with the published statistical analysis plan using a modified intention-to-treat principle after the exclusion of patients who had withdrawn consent, had been lost to follow-up, or had undergone randomization but had subsequently been found to be ineligible.[11] On the basis of an assumed 90-day mortality of 40% in the standard-strategy group, we calculated that the enrollment of 2866 patients would provide a power of 90% to detect a 15% relative between-group difference (absolute difference, 6 percentage points) in the primary outcome at a two-sided signifi-

cance level of 0.05, while allowing for 3% attrition (withdrawal of consent, loss to follow-up, or crossover).[6,17] To compensate for such attrition, we revised recruitment to 3000 patients. In the United Kingdom, enrollment was extended to meet local recruitment targets. The expansion in recruitment was approved by the data and safety monitoring board.

We evaluated the primary outcome of death at 90 days using a chi-square test, with the results reported as a relative risk and absolute risk difference with 95% confidence intervals. Death at 90 days was also reported in an adjusted logistic-regression analysis as an odds ratio with 95% confidence intervals and in a Kaplan–Meier time-to-event analysis in which data were censored at 90 days and compared with the use of a log-rank test. We performed prespecified exploratory analyses of the primary outcome (Table S3) and conducted prespecified subgroup analyses of the primary outcome for six variables: sex, baseline eGFR, baseline SAPS II, surgical admission, the presence of sepsis, and geographic region.[18]

We reported secondary outcomes — including dependence on renal-replacement therapy, a composite of death or dependence on renal-replacement therapy, and a major adverse kidney event at 90 days — as unadjusted relative risks with 95% confidence intervals and performed between-group comparisons using a chi-square test. We used inverse probability weighting and multinomial regression to account for postrandomization selection bias when evaluating continuing dependence on renal-replacement therapy (Table S3). We used a t-test to compare serum creatinine levels and eGFR values among survivors at 90 days. We calculated medians and interquartile ranges to summarize the number of days that patients were alive and free of renal-replacement therapy, the use of vasoactive drugs or mechanical ventilation, ICU stay, hospital stay, and quality of life according to treatment group. We used linear regression to perform between-group comparisons and reported the results as mean differences and 95% confidence intervals. The statistical analysis plan did not include a provision that secondary analyses would be corrected for multiple comparisons.[11] As such, the 95% confidence intervals have not been adjusted for multiplicity and should not be used to infer definitive treatment effects for secondary outcomes. All statistical analyses were performed with the use of Stata software, version 15, and R software, version 3.6.2.[19]

RESULTS

PATIENTS

From October 2015 through September 2019, a total of 11,852 patients met provisional eligibility. Of these patients, 3019 were randomly assigned to receive either an accelerated strategy for the initiation of renal-replacement therapy (1512 patients) or a standard strategy (1507 patients) (Fig. S2). The number of patients who were subsequently determined to be ineligible to participate were 31 (2.1%) in the accelerated-strategy group and 19 (1.3%) in the standard-strategy group (Table S4). In the accelerated-strategy group, 9 patients (0.6%) withdrew consent and 7 (0.5%) were lost to follow-up; the corresponding numbers in the standard-strategy group were 18 (1.2%) and 8 (0.5%). Thus, 2927 patients (1465 in the accelerated-strategy group and 1462 in the standard-strategy group) were included in the modified intention-to-treat analysis.

Baseline characteristics were well balanced in the two groups (Table 1 and Table S5). In the entire population, chronic kidney disease was present in 1284 patients (43.9%); 965 patients (33.0%) had been admitted to undergo surgery, 1689 patients (57.7%) had sepsis, and the mean (±SD) SAPS II and SOFA scores were 58.8±17.4 and 11.7±3.6, respectively.

INITIATION OF RENAL-REPLACEMENT THERAPY

In the accelerated-strategy group, renal-replacement therapy was initiated at a median of 6.1 hours (interquartile range, 3.9 to 8.8) after the determination of full eligibility in 1418 of 1465 patients (96.8%). In the standard-strategy group, such therapy was initiated in 903 of 1462 patients (61.8%) at a median of 31.1 hours (interquartile range, 19.0 to 71.8) after the determination of full eligibility (Fig. S3). The characteristics of the patients at the time of renal-replacement therapy and features of the initial prescription are provided in Tables S6 and S7. Among the patients in the standard-strategy group who underwent renal-replacement therapy, 597 of 903 (66.1%) fulfilled at least one prespecified indication for the initiation of such therapy. At the time of initiation, the SOFA score, serum creatinine level, blood urea nitrogen level, and positive

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Accelerated Strategy (N = 1465)	Standard Strategy (N = 1462)
Age — yr	64.6±14.3	64.7±13.4
Female sex — no. (%)	470 (32.1)	467 (31.9)
Weight — kg	88.0±27.4	88.0±25.1
Serum creatinine — mg/dl†	1.4±1.0	1.3±1.0
Estimated glomerular filtration rate — ml/min/1.73 m²‡	66.0±29.8	67.3±29.8
Preexisting conditions — no./total no. (%)		
Chronic kidney disease	658/1465 (44.9)	626/1462 (42.8)
Hypertension	814/1465 (55.6)	823/1462 (56.3)
Diabetes mellitus	439/1465 (30.0)	459/1461 (31.4)
Heart failure	204/1465 (13.9)	204/1461 (14.0)
Coronary artery disease	320/1465 (21.8)	328/1461 (22.5)§
Liver disease	172/1465 (11.7)	165/1461 (11.3)
Metastatic cancer	77/1465 (5.3)	84/1462 (5.7)
Hematologic cancer	87/1465 (5.9)	83/1462 (5.7)
HIV infection or AIDS	13/1465 (0.9)	13/1462 (0.9)
Admission category — no. (%)		
Scheduled surgery	207 (14.1)	184 (12.6)
Unscheduled surgery	285 (19.5)	289 (19.8)
Medical	973 (66.4)	989 (67.6)
Hospital-acquired risk factor for AKI in previous wk — no./total no. (%)		
Cardiopulmonary bypass	112/1465 (7.6)	118/1462 (8.1)
Aortic aneurysm repair	71/1465 (4.8)	74/1461 (5.1)
Other vascular surgery	76/1465 (5.2)	77/1462 (5.3)
Major trauma	62/1465 (4.2)	55/1462 (3.8)
Obstetric complication	5/1465 (0.3)	5/1462 (0.3)
Exposure to radiocontrast material	382/1463 (26.1)	375/1460 (25.7)
Receipt of aminoglycoside	154/1463 (10.5)	148/1458 (10.2)
Receipt of amphotericin B	9/1464 (0.6)	12/1460 (0.8)
Clinical condition at randomization		
Sepsis — no. (%)	855 (58.4)	834 (57.0)
Septic shock — no. (%)	640 (43.7)	643 (44.0)
SAPS II value¶	58.1±17.4	59.4±17.4
SOFA score‖	11.6±3.6	11.8±3.6
Mechanical ventilation — no. (%)	1103 (75.3)	1148 (78.5)
Vasoactive support — no. (%)	1008 (68.8)	1052 (72.0)
Serum creatinine — mg/dl	3.6±1.7	3.4±1.6
Serum potassium — mmol/liter	4.5±0.8	4.5±0.8
Serum bicarbonate — mmol/liter	19.7±4.7	19.5±4.5
Median urinary output (IQR) — ml/24 hr**	450 (190–945)	478 (187–975)
Oliguria or anuria — no./total no. (%)††	647/1415 (45.7)	618/1420 (43.5)

Table 1. (Continued.)		
Characteristic	Accelerated Strategy (N = 1465)	Standard Strategy (N = 1462)
Median cumulative fluid balance (IQR) — ml‡‡	2581 (820–5362)	2819 (836–5603)

* Plus–minus values are means ±SD. Listed are data in the modified intention-to-treat population. To convert the values for creatinine to micromoles per liter, multiply by 88.4. AIDS denotes acquired immunodeficiency syndrome, AKI acute kidney injury, HIV human immunodeficiency virus, and IQR interquartile range.

† At baseline, the serum creatinine level was defined as the most recent outpatient level obtained during the year preceding the current hospitalization. If this value was not available, the lowest serum creatinine level obtained during the current hospitalization was used to establish the baseline.

‡ The estimated glomerular filtration rate was calculated with the use of the Chronic Kidney Disease Epidemiology Collaboration equation, which incorporates the baseline serum creatinine level, age, sex, and black race.

§ Data in this category were missing for 1 patient in the standard-strategy group.

¶ Results for the Simplified Acute Physiology Score (SAPS) II range from 0 to 163, with higher scores indicating more severe disease and a higher risk of death.

‖ Scores on the Sequential Organ Failure Assessment (SOFA) range from 0 to 24, with higher scores indicating more severe disease and a higher risk of death.

** Data regarding urinary output were available for 2835 of 2927 patients (96.9%) who had collection of data for at least 24 hours.

†† Oliguria was defined as a urinary output of less than 400 ml per 24-hour period.

‡‡ Data regarding cumulative fluid balance after admission to an intensive care unit were available for 2738 of 2927 patients (93.5%): 1378 in the accelerated-strategy group and 1360 in the standard-strategy group..

fluid balance were higher among the patients in the standard-strategy group than among those in the accelerated-strategy group.

PRIMARY OUTCOME

In the modified intention-to-treat analysis, death at 90 days occurred in 643 patients (43.9%) in the accelerated-strategy group and in 639 (43.7%) in the standard-strategy group (relative risk, 1.00; 95% confidence interval [CI], 0.93 to 1.09), for an absolute risk difference of 0.2 percentage points (95% CI, −0.3 to 0.4; P=0.92) (Table 2, Fig. 1, and Fig. S4). Results were similar in the adjusted analysis (adjusted odds ratio, 1.05; 95% CI, 0.90 to 1.23).

SECONDARY OUTCOMES

Among the patients who were alive at 90 days, continued dependence on renal-replacement therapy was determined in 85 of 814 (10.4%) in the accelerated-strategy group and in 49 of 815 (6.0%) in the standard-strategy group (relative risk, 1.74; 95% CI, 1.24 to 2.43). This result was robust after inverse probability weighting and in a multinomial analysis (Table S8).

There was no meaningful between-group difference in the composite of death or dependence on renal-replacement therapy, major adverse kidney events at 90 days, death in the ICU at 28 days, or length of hospitalization (Table 2). In addi-tion, there were no substantial between-group differences in the causes of death (Table S9). In each group, patients had a similar number of days free of renal-replacement therapy at 90 days; there were marginally fewer days of renal-replacement therapy among the patients in the accelerated-strategy group than among those in the standard-strategy group (−0.48 days; 95% CI, −0.82 to −0.14). Patients in the accelerated-strategy group had a shorter ICU stay than those in the standard-strategy group, but there was no evidence of large between-group differences in the number of ventilator-free days, vasoactive-free days, or ICU-free days at 28 days. Patients in the accelerated-strategy group had a higher risk of rehospitalization (relative risk, 1.23; 95% CI, 1.02 to 1.49), but there was no evidence of a large between-group difference in the number of hospitalization-free days at 90 days. Among survivors, measures of quality of life and functional domains were similar.

SUBGROUP ANALYSES

There was no evidence of substantial between-group heterogeneity of treatment effect regarding 90-day mortality across prespecified subgroups (Fig. 2 and Tables S10 and S11). Similarly, there was no evidence of substantial heterogeneity of treatment effect on 90-day mortality across SAPS II scores at the time of enrollment (Fig. S5).

Table 2. Primary and Secondary Outcomes.*

	Accelerated Strategy (N = 1465)	Standard Strategy (N = 1462)	Relative Risk or Difference (95% CI)
Primary outcome			
Death from any cause at 90 days — no. (%)†	643 (43.9)	639 (43.7)	1.00 (0.93 to 1.09)‡
Secondary outcomes			
RRT dependence among survivors at 90 days — no./total no. (%)	85/814 (10.4)	49/815 (6.0)	1.74 (1.24 to 2.43)‡
Death or RRT dependence at 90 days — no./total no. (%)	728/1457 (50.0)	688/1454 (47.3)	1.06 (0.98 to 1.14)‡
Major adverse kidney events at 90 days — no./total no. (%)	867/1131 (76.7)	860/1115 (77.1)	0.99 (0.95 to 1.04)‡
Serum creatinine at 90 days — mg/dl§	1.20±1.00	1.23±1.00	−0.03 (−0.11 to 0.06)¶
Estimated glomerular filtration rate‖			
At 90 days — ml/min/1.73 m²	65±30	64±31	0.31 (−3.88 to 4.49)¶
Reduction of >25% from baseline at 90 days — no./total no. (%)	139/403 (34.5)	172/427 (40.3)	0.86 (0.72 to 1.02)‡
Death from any cause — no./total no. (%)			
At any time in the ICU	461/1464 (31.5)	468/1462 (32.0)	0.98 (0.88 to 1.09)‡
At 28 days	538/1465 (36.7)	523/1462 (35.8)	1.03 (0.93 to 1.13)‡
During hospitalization	552/1458 (37.9)	546/1459 (37.4)	1.01 (0.92 to 1.11)‡
Use of health services			
Median no. of days of use (IQR)			
RRT-free days at 90 days**	50 (0 to 87)	64 (0 to 90)	−2.62 (−5.66 to 0.42)¶
RRT††	4 (2 to 8)	5 (3 to 9)	−0.48 (−0.82 to −0.14)¶
Continuous RRT††	4 (3 to 8)	5 (3 to 8)	−0.40 (−0.78 to −0.02)¶
Sustained low-efficiency dialysis††	2 (1 to 4)	2 (1 to 4)	0.15 (−0.65 to 0.96)¶
Intermittent hemodialysis††	2 (1 to 4)	3 (2 to 5)	−0.45 (−0.80 to −0.09)¶
Median length of stay in ICU (IQR) — days			
Survivors	9 (5 to 16)	10 (5 to 19)	−1.58 (−2.90 to −0.26)¶
Nonsurvivors	7 (3 to 13)	7 (4 to 15)	−1.33 (−2.56 to −0.09)¶
Median length of hospital stay (IQR) – days			
Survivors	28 (16 to 50)	29 (17 to 54)	−1.23 (−3.87 to 1.41)¶
Nonsurvivors	8 (3 to 18)	9 (4 to 19)	−0.99 (−2.66 to 0.67)¶
Median no. of ventilator-free days at 28 days (IQR)	13 (0 to 24)	12 (0 to 24)	0.50 (−0.34 to 1.35)¶
Median no. of days free of vasoactive agents at 28 days (IQR)	21 (0 to 26)	20 (0 to 26)	0.31 (−0.57 to 1.18)¶
Median no. of days out of ICU at 28 days (IQR)	8 (0 to 21)	4 (0 to 20)	0.69 (−0.06 to 1.43)¶
Median no. of days out of hospital at 90 days (IQR)	10 (0 to 65)	9 (0 to 64)	0.55 (−1.82 to 2.91)¶
Rehospitalization at 90 days — no./total no. (%)	191/913 (20.9)	156/916 (17.0)	1.23 (1.02 to 1.49)‡
Health-related quality of life			
Median score on EQ-5D-5L at 90 days (IQR)			
Descriptive system‡‡			
Mobility	2 (1 to 3)	2 (1 to 3)	−0.07 (−0.23 to 0.08)¶
Self care	1 (1 to 3)	1 (1 to 3)	−0.10 (−0.25 to 0.05)¶
Usual activities	2 (1 to 3)	2 (1 to 4)	−0.15 (−0.31 to 0.01)¶
Pain or discomfort	2 (1 to 3)	2 (1 to 3)	−0.04 (−0.17 to 0.08)¶
Anxiety or depression	1 (1 to 3)	2 (1 to 3)	−0.06 (−0.19 to 0.07)¶

Table 2. (Continued.)			
	Accelerated Strategy (N = 1465)	Standard Strategy (N = 1462)	Relative Risk or Difference (95% CI)
EQ-VAS§§	70 (50 to 80)	70 (50 to 80)	0.11 (−2.55 to 2.76)¶
Score of >4 on Clinical Frailty Scale at 90 days — no. (%)¶¶	213/655 (32.5)	227/647 (35.1)	0.93 (0.80 to 1.08)‡

* Plus–minus values are means ±SD. ICU denotes intensive care unit, and RRT renal-replacement therapy.
† P=0.92 for the primary outcome. P values were not calculated for the secondary outcomes because comparisons were not adjusted for multiple comparisons.
‡ This value is expressed as a relative risk.
§ Data regarding serum creatinine levels are for survivors at 90 days who were not dependent on kidney-replacement therapy. Of these 1511 patients, data were available for 830 (54.9%): 403 patients in the accelerated-strategy group and 427 patients in the standard-strategy group.
¶ This value is expressed as a mean difference.
‖ The estimated glomerular filtration rate was calculated with the Chronic Kidney Disease Epidemiology Collaboration equation.
** Data regarding RRT-free days are provided for 2900 of 2927 (99.0%) patients: 1448 in the accelerated-strategy group and 1452 in the standard-strategy group.
†† Included in this category are patients who received renal-replacement therapy.
‡‡ On the European Quality of Life–5-Dimensions 5-Level questionnaire (EQ-5D-5L), scores for each of the five domains of the descriptive system range from 1 to 5, with higher scores representing greater impairment or worse function. Scores at 90 days were available for 1164 of 1645 patients (70.8%) for the mobility domain (581 patients in the accelerated-strategy group and 583 patients in the standard-strategy group); 1165 of 1645 (70.8%) for the self-care domain (582 patients and 583 patients, respectively); 1163 of 1645 (70.7%) for the usual activities domain (581 patients and 582 patients, respectively); 1162 of 1645 (70.6%) for the pain or discomfort domain (580 patients and 582 patients, respectively); and 1153 of 1645 (70.1%) for the anxiety or depression domain (576 patients and 577 patients, respectively).
§§ Scores on the Visual Analogue Scale of the EQ-5D-5L questionnaire (EQ-VAS) range from 0 to 100, with higher scores indicating better health. EQ-VAS scores were available for 1103 of 1645 survivors (67.0%) at 90 days: 555 patients in the accelerated-strategy group and 548 in the standard-strategy group.
¶¶ Scores on the Clinical Frailty Scale range from 1 to 9, with higher scores indicating a higher degree of frailty. A score of more than 4 is the threshold for the definition of frailty. Scores on this scale at 90 days were available for 1302 of 1645 survivors (79.1%).
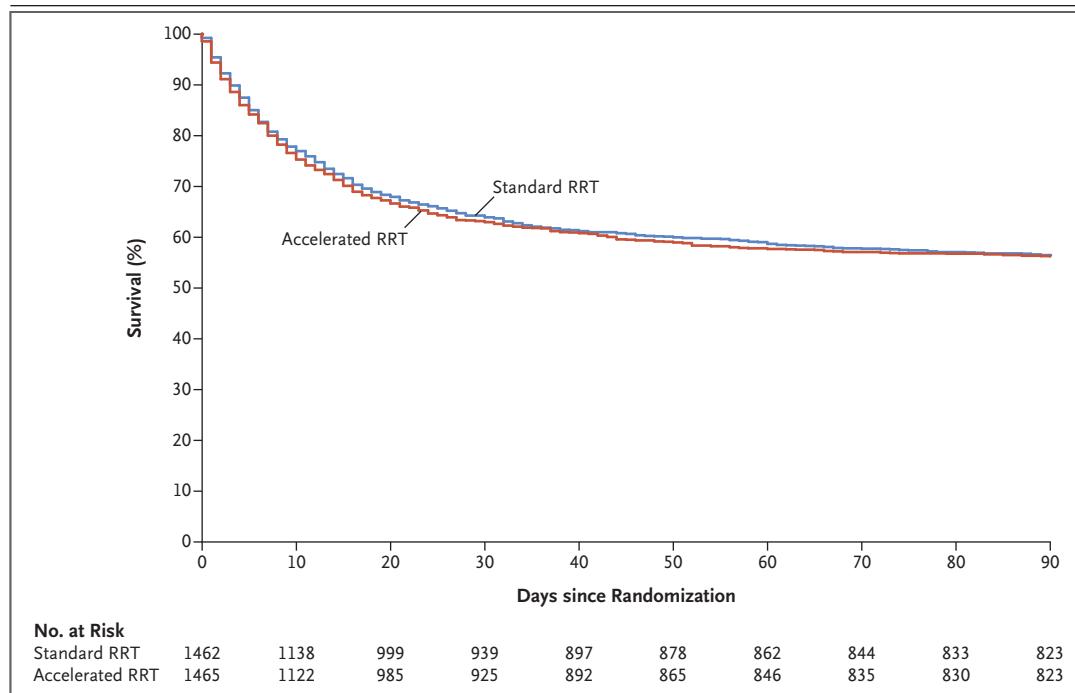

No. at Risk										
Standard RRT	1462	1138	999	939	897	878	862	844	833	823
Accelerated RRT	1465	1122	985	925	892	865	846	835	830	823

Figure 1. Kaplan–Meier Estimates of Survival at 90 Days.

In the modified intention-to-treat analysis, death at 90 days occurred in 643 patients (43.9%) in the group that received an accelerated strategy for renal-replacement therapy (RRT) and in 639 (43.7%) in the group that received a standard strategy, for an absolute risk difference of 0.2 percentage points (P=0.92). P=0.75 for the between-group difference in the Kaplan–Meier time-to-event analysis.
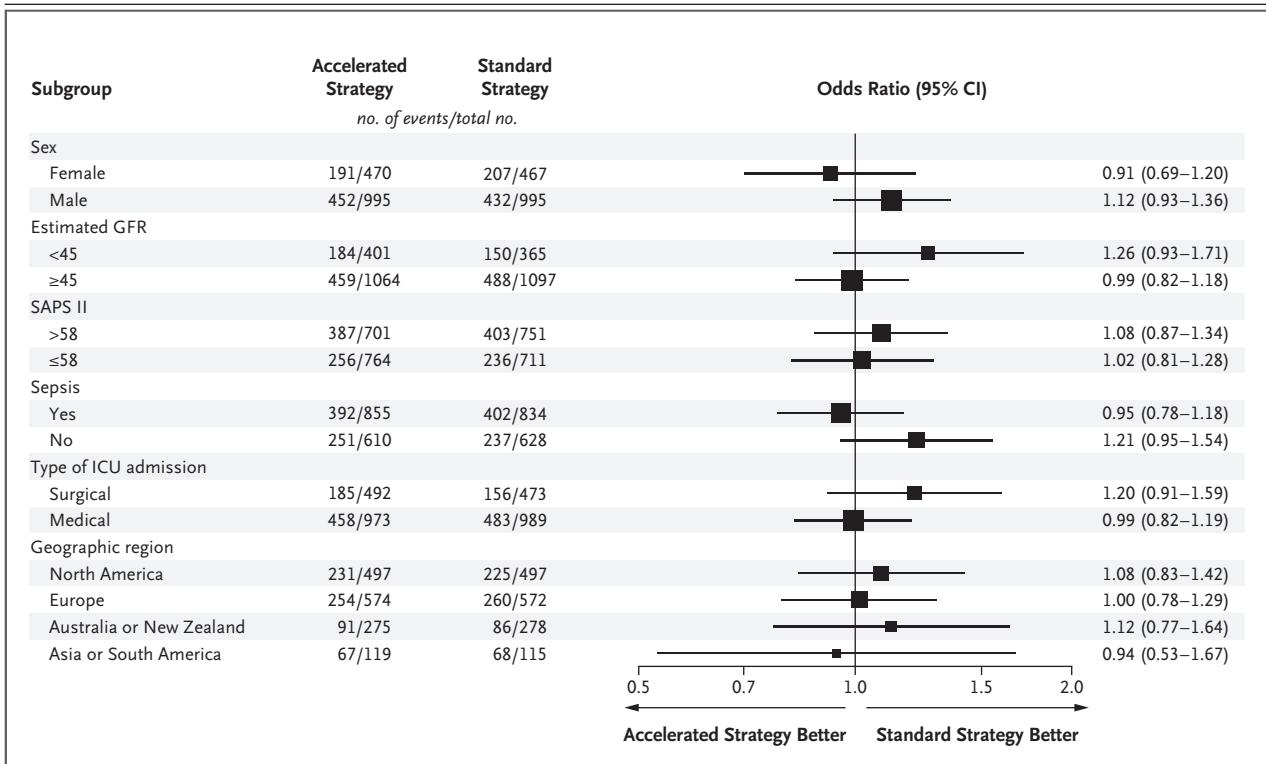
Subgroup	Accelerated Strategy	Standard Strategy	Odds Ratio (95% CI)	
	no. of events/total no.			
Sex				
Female	191/470	207/467		0.91 (0.69–1.20)
Male	452/995	432/995		1.12 (0.93–1.36)
Estimated GFR				
<45	184/401	150/365		1.26 (0.93–1.71)
≥45	459/1064	488/1097		0.99 (0.82–1.18)
SAPS II				
>58	387/701	403/751		1.08 (0.87–1.34)
≤58	256/764	236/711		1.02 (0.81–1.28)
Sepsis				
Yes	392/855	402/834		0.95 (0.78–1.18)
No	251/610	237/628		1.21 (0.95–1.54)
Type of ICU admission				
Surgical	185/492	156/473		1.20 (0.91–1.59)
Medical	458/973	483/989		0.99 (0.82–1.19)
Geographic region				
North America	231/497	225/497		1.08 (0.83–1.42)
Europe	254/574	260/572		1.00 (0.78–1.29)
Australia or New Zealand	91/275	86/278		1.12 (0.77–1.64)
Asia or South America	67/119	68/115		0.94 (0.53–1.67)

0.5   0.7   1.0   1.5   2.0

← Accelerated Strategy Better   Standard Strategy Better →

Figure 2. Subgroup Analyses.

Shown is a forest plot of the risk of the primary outcome (death from any cause at 90 days) in the accelerated-strategy group and the standard-strategy group. The size of the square representing the odds ratio reflects the relative number of patients in each subgroup. Results for the Simplified Acute Physiology Score (SAPS) II range from 0 to 163, with higher scores indicating more severe disease and a higher risk of death. GFR denotes glomerular filtration rate, and ICU intensive care unit.

SENSITIVITY ANALYSIS OF THE PRIMARY OUTCOME

In the as-treated analysis, there was no evidence of a between-group difference in 90-day mortality. Death was reported in 623 of 1418 patients (43.9%) in the accelerated-strategy group and in 659 of 1509 (43.7%) in the standard-strategy group (unadjusted odds ratio, 1.01; 95% CI, 0.87 to 1.17).

ADVERSE EVENTS

Adverse events occurred in 346 of 1503 patients (23.0%) in the accelerated-strategy group and in 245 of 1489 patients (16.5%) in the standard-strategy group (risk ratio, 1.40; 95% CI, 1.21 to 1.62; P<0.001) (Table 3). Hypotension and hypophosphatemia were the most common adverse events with a significant between-group difference. There was no difference in serious adverse events between the two strategies.

DISCUSSION

In this large, multinational, randomized trial, critically ill patients with severe acute kidney injury who received an accelerated strategy for the initiation of renal-replacement therapy did not have a lower risk of death at 90 days than those who received a standard strategy. This finding clarifies a long-standing clinical dilemma regarding the treatment strategy for critically ill patients with acute kidney injury who have no overt complications that would mandate the immediate initiation of renal-replacement therapy.[20] Observational studies using various biochemical thresholds as surrogates for the timing of initiation and a single-center randomized trial that enrolled primarily surgical patients suggested that earlier renal-replacement therapy resulted in a lower mortality than delayed therapy.[7,21-23]

Table 3. Adverse Events.*

Adverse Events	Accelerated Strategy (N = 1503)		Standard Strategy (N = 1489)		P Value†
	Patients	Events	Patients	Events	
	no. (%)	no. (per 1000 patient-mo)	no. (%)	no. (per 1000 patient-mo)	
Any adverse event	346 (23.0)	556 (195.7)	245 (16.5)	364 (128.1)	<0.001
Associated with renal-replacement therapy					
Hypotension	131 (8.7)	188 (66.2)	83 (5.6)	112 (39.4)	0.001
Arrhythmia	37 (2.5)	45 (15.8)	23 (1.5)	29 (10.2)	0.07
Seizure	1 (0.1)	1 (0.4)	0	0	1.00
Bleeding	4 (0.3)	4 (1.4)	1 (0.1)	1 (0.4)	0.37
Allergic reaction	1 (0.1)	1 (0.4)	1 (0.1)	1 (0.4)	1.00
Decreased phosphate (<0.5 mmol/liter)	112 (7.5)	124 (43.7)	62 (4.2)	68 (23.9)	<0.001
Decreased potassium (<3.0 mmol/liter)	34 (2.3)	43 (15.1)	34 (2.3)	40 (14.1)	0.97
Decreased ionized calcium (<0.90 mmol/ liter)	80 (5.3)	102 (35.9)	66 (4.4)	80 (28.1)	0.26
Associated with use of a dialysis catheter					
Pneumothorax or hemothorax	4 (0.3)	5 (1.8)	2 (0.1)	2 (0.7)	0.69
Bleeding	6 (0.4)	6 (2.1)	4 (0.3)	4 (1.4)	0.75
Thrombus (as confirmed on ultrasonography)	3 (0.2)	3 (1.1)	5 (0.3)	5 (1.8)	0.51
Arterial puncture	3 (0.2)	3 (1.1)	2 (0.1)	2 (0.7)	1.00
Bloodstream infection	7 (0.5)	7 (2.5)	1 (0.1)	1 (0.4)	0.07
Other	21 (1.4)	24 (8.4)	20 (1.3)	19 (6.7)	0.90
Serious adverse events — no. (%)	15 (1.0)	17 (6.0)	8 (0.5)	8 (2.8)	0.15

* Listed are data through 14 days for 2992 of 3019 patients (99.1%) who had undergone randomization and remained in the ICU; not included are 27 patients for whom consent had been withdrawn. Individual investigators made the determination of whether the adverse event was related to renal-replacement therapy or the use of a dialysis catheter. To convert the values for phosphate to milligrams per deciliter, divide by 0.3229. To convert the values for potassium to milligrams per deciliter, divide by 0.2558. To convert the values for ionized calcium to milligrams per deciliter, divide by 0.250.
† P values are for the between-group difference in the percentage of patients with a specific adverse event and have not been adjusted for multiple comparisons.

Conversely, two multicenter, randomized trials, including one that exclusively involved patients with septic shock, did not show a lower risk of death with an early strategy than with a delayed strategy for the initiation of renal-replacement therapy.[4,5] In these two trials, eligibility was tied to fulfilling consensus-defined serum creatinine levels and urine-output thresholds for severe acute kidney injury, with renal-replacement therapy initiated promptly after this determination in the early-therapy group. In the delayed-therapy group, the initiation of renal-replacement therapy was mandated for patients in whom acute kidney injury persisted for 48 to 72 hours or in whom metabolic or fluid complications developed. In the two trials, a sizable percentage of patients in the delayed-therapy group did not receive renal-replacement therapy because they either recovered kidney function or died.

In our trial, we aimed to enrich our patient population by incorporating clinical equipoise to guide eligibility, rather than relying on defined intervals after the patients fulfilled consensus criteria for severe acute kidney injury. This process excluded more than 7000 patients who had been rated by clinicians as being appropriate candidates for emergency renal-replacement therapy or likely to have imminent recovery of kidney

function. Furthermore, triggers for the initiation of renal-replacement therapy in our standard-strategy group were not directed by thresholds for severity of acute kidney injury or defined time intervals.[4,5,7] Our trial also provided evidence-informed recommendations for the prescription of renal-replacement therapy and adopted a pragmatic approach to reflect current practice. Similar to our pilot work and previous trials, a substantial percentage of the patients in the standard-strategy group did not receive renal-replacement therapy, which highlights the challenge faced by clinicians in predicting worsening acute kidney injury in critically ill patients.[4-6] Despite these differences in trial design, we did not observe a lower 90-day mortality with an accelerated strategy, a finding that was robust in adjusted and sensitivity analyses.

A greater percentage of survivors who received the accelerated strategy were dependent on renal-replacement therapy at 90 days and had adverse events. This finding suggests that greater exposure to renal-replacement therapy, possibly modified according to baseline risk (e.g., the presence of chronic kidney disease) or mediated by iatrogenic factors (e.g., hypotension), may compromise kidney repair and the return of endogenous kidney function.[24-26]

There are noteworthy strengths of our trial. First, our large sample size afforded the ability to detect a clinically important difference in mortality between accelerated and standard initiation of renal-replacement therapy. Second, the recruitment of patients from a wide spectrum of ICUs in several countries enabled broad generalizability. Third, our trial deliberately enrolled patients for whom the decision on the initiation of renal-replacement therapy was genuinely uncertain by excluding those for whom treating clinicians felt a lack of equipoise.[6]

Our trial also has limitations. First, we recognize that equipoise is relatively subjective and that the perception of equipoise may be modified by individual clinician bias. By allowing clinicians to use their judgment in confirming full eligibility, we may have introduced patient heterogeneity into the trial. However, we did not observe evidence of substantial heterogeneity of treatment effect across subgroups, including illness severity and geographic region. Second, although the protocol provided recommendations on when to start renal-replacement therapy in patients in the standard-strategy group, the broad discretion that was afforded to clinicians may have resulted in variable initiation times. Third, adverse events were more frequent with the accelerated strategy, although this result may be partly attributed to the prespecified focus on reporting of events related to renal-replacement therapy and to the larger number of patient-days of such therapy with this strategy.

In conclusion, in critically ill patients with severe acute kidney injury, an accelerated strategy for the initiation of renal-replacement therapy did not result in a lower mortality at 90 days than a standard strategy.

APPENDIX

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