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Intensity of Continuous Renal-Replacement Therapy in Critically Ill Patients

The RENAL Replacement Therapy Study Investigators*

ABSTRACT

BACKGROUND

The optimal intensity of continuous renal-replacement therapy remains unclear. We conducted a multicenter, randomized trial to compare the effect of this therapy, delivered at two different levels of intensity, on 90-day mortality among critically ill patients with acute kidney injury.

METHODS

We randomly assigned critically ill adults with acute kidney injury to continuous renal-replacement therapy in the form of postdilution continuous venovenous hemodiafiltration with an effluent flow of either 40 ml per kilogram of body weight per hour (higher intensity) or 25 ml per kilogram per hour (lower intensity). The primary outcome measure was death within 90 days after randomization.

RESULTS

Of the 1508 enrolled patients, 747 were randomly assigned to higher-intensity therapy, and 761 to lower-intensity therapy with continuous venovenous hemodiafiltration. Data on primary outcomes were available for 1464 patients (97.1%): 721 in the higher-intensity group and 743 in the lower-intensity group. The two study groups had similar baseline characteristics and received the study treatment for an average of 6.3 and 5.9 days, respectively (P=0.35). At 90 days after randomization, 322 deaths had occurred in the higher-intensity group and 332 deaths in the lower-intensity group, for a mortality of 44.7% in each group (odds ratio, 1.00; 95% confidence interval [CI], 0.81 to 1.23; P=0.99). At 90 days, 6.8% of survivors in the higher-intensity group (27 of 399), as compared with 4.4% of survivors in the lower-intensity group (18 of 411), were still receiving renal-replacement therapy (odds ratio, 1.59; 95% CI, 0.86 to 2.92; P=0.14). Hypophosphatemia was more common in the higher-intensity group than in the lower-intensity group (65% vs. 54%, P<0.001).

CONCLUSIONS

In critically ill patients with acute kidney injury, treatment with higher-intensity continuous renal-replacement therapy did not reduce mortality at 90 days. (ClinicalTrials.gov number, NCT00221013.)

The Randomized Evaluation of Normal versus Augmented Level (RENAL) Replacement Therapy Study is a collaboration of the Australian and New Zealand Intensive Care Society Clinical Trials Group and the George Institute for International Health. The members of the Writing Committee for the RENAL Replacement Therapy Study (Rinaldo Bellomo, M.D., Alan Cass, M.D., Ph.D., Louise Cole, M.D., Ph.D., Simon Finfer, M.D., Martin Gallagher, M.D., Serigne Lo, Ph.D., Colin McArthur, M.D., Shay McGuinness, M.D., John Myburgh, M.D., Ph.D., Robyn Norton, M.D., Ph.D., M.P.H., Carlos Scheinkestel, M.D., and Steve Su, Ph.D.) take responsibility for the content of this article. Address reprint requests to Dr. Bellomo at ANZICS CTG, Level 3, 10 Ievers St., Carlton, VIC 3053, Australia, or at ctg@anzics.com.au.

*The members of the Randomized Evaluation of Normal versus Augmented Level (RENAL) Replacement Therapy Study Group and their affiliations are listed in the Appendix.

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Acute kidney injury is associated with substantial morbidity and mortality.[1] It is a common finding among patients in the intensive care unit (ICU)[2] and is an independent predictor of mortality.[3] Acute kidney injury severe enough to result in the use of renal-replacement therapy affects approximately 5% of patients admitted to the ICU and is associated with a mortality rate of 60%.[4] The optimal approach to renal-replacement therapy, as well as the optimal intensity and timing of such therapy, in critically ill patients remains unclear. In one single-center, randomized, controlled study in which continuous renal-replacement therapy was the sole treatment approach, survival improved when the intensity of therapy was increased from an assigned effluent rate of 20 ml per kilogram of body weight per hour to either 35 or 45 ml per kilogram per hour.[5] However, subsequent single-center studies have had conflicting results.[6-8]

The recently reported Veterans Affairs/National Institutes of Health Acute Renal Failure Trial Network Study (ClinicalTrials.gov number, NCT00076219)[9] showed that increasing the intensity of renal-replacement therapy did not decrease mortality among patients with acute kidney injury. In contrast to other studies, which used continuous renal-replacement therapy exclusively, this study assigned patients to a protocol of either intermittent or continuous renal-replacement therapy according to whether they were hemodynamically stable or unstable, respectively. This design reflects clinical practice in the United States and elsewhere but makes it difficult to carry out a formal comparison of treatment intensities that would be independent of the particular treatment approach. We conducted a randomized, controlled study to test the hypothesis that increasing the intensity of continuous renal-replacement therapy would reduce mortality at 90 days.

Methods

Study Design

The Randomized Evaluation of Normal versus Augmented Level (RENAL) Replacement Therapy Study was a prospective, randomized, parallel-group trial designed to assess two levels of intensity of continuous renal-replacement therapy in critically ill patients with acute kidney injury. The study was conducted between December 30, 2005, and November 28, 2008, in 35 ICUs in Australia and New Zealand. The study protocol is outlined in the Supplementary Appendix, available with the full text of this article at NEJM.org. It was approved by the human research ethics committees of the University of Sydney and all participating institutions. The integrity of data collection was verified by the George Institute for International Health monitoring team. An independent data and safety monitoring committee reviewed safety data and interim results with the aim of providing advice to the trial management committee should such analyses prove beyond a reasonable doubt that augmented continuous renal-replacement therapy led to a net benefit or harm in terms of mortality.

Study Population

Patients were eligible for enrollment if they were critically ill, were 18 years of age or older, had acute kidney injury, were deemed by the treating clinician to require renal-replacement therapy, and met at least one of the following criteria: oliguria (urine output <100 ml in a 6-hour period) that was unresponsive to fluid resuscitation measures, a serum potassium concentration exceeding 6.5 mmol per liter, severe acidemia (pH <7.2), a plasma urea nitrogen level above 70 mg per deciliter (25 mmol per liter), a serum creatinine concentration above 3.4 mg per deciliter (300 μmol per liter), or the presence of clinically significant organ edema (e.g., pulmonary edema). Written informed consent was obtained from the patient or responsible surrogate by means of either a priori or delayed consent. (For a detailed description of delayed consent, see the Supplementary Appendix.)

Patients who had received any previous renal-replacement therapy during the same hospital admission or who were on maintenance dialysis for end-stage kidney disease were ineligible for the study. (For a detailed list of inclusion and exclusion criteria and the criteria for discontinuing the study treatment, see the Supplementary Appendix.)

Intervention

The patients in both groups were treated with continuous venovenous hemodiafiltration. Replacement fluid was delivered into the extracorporeal circuit after the filter (i.e., postdilution), with a ratio of dialysate to replacement fluid of 1:1. The effluent flow prescribed was based on the patient's body weight at the time of randomization and was either 40 ml per kilogram per hour (for the higher-

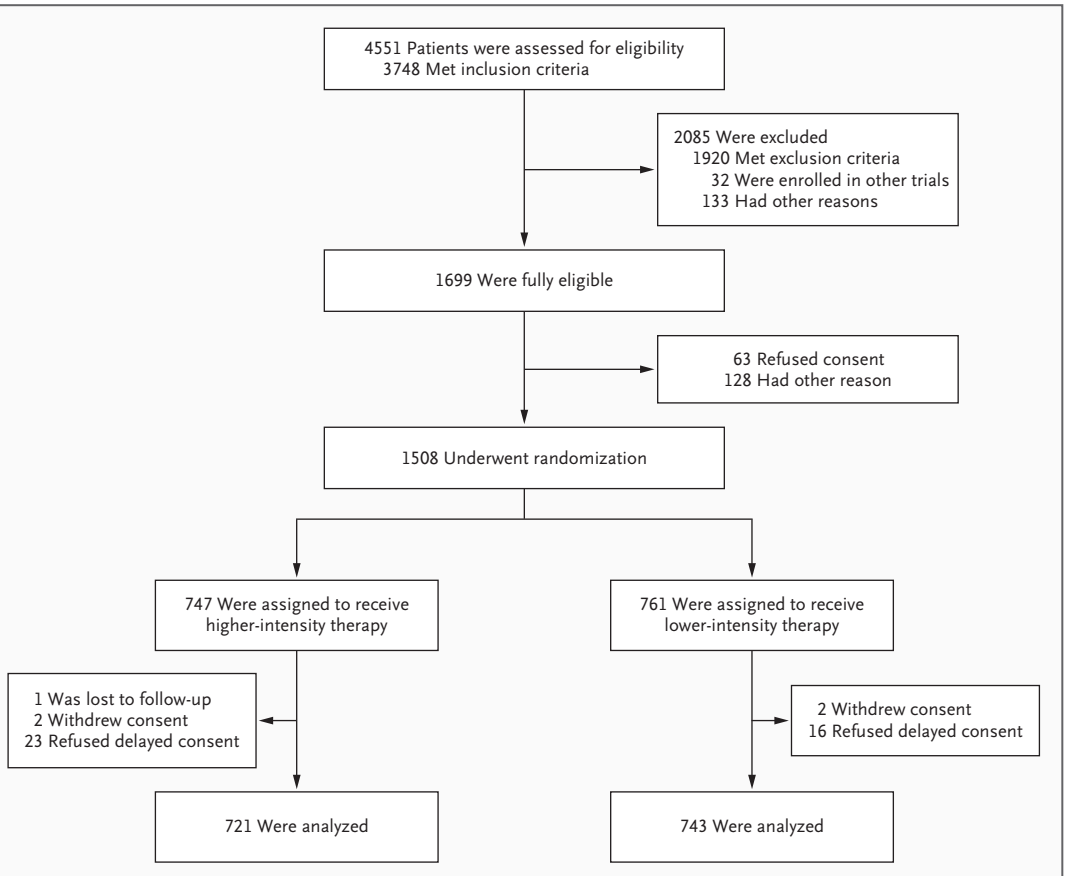

Figure 1. Numbers of Patients Enrolled in the Study, Randomly Assigned to a Treatment Group, and Included in the Analysis.

intensity group) or 25 ml per kilogram per hour (for the lower-intensity group). Blood flow was kept above 150 ml per minute. Fluid was removed by decreasing the flow of the replacement fluid and of the dialysate in equal proportion, so that effluent exceeded them both by any amount prescribed by the clinician. Filters with the AN69 membrane (Gambro) were used. Hemosol BO fluid (Gambro) was used as the dialysate and replacement fluid. Gambro had no role in the initiation, design, analysis, or reporting of the study.

STUDY OUTCOMES

The primary study outcome was death from any cause within 90 days after randomization. Secondary and tertiary outcomes included death within 28 days after randomization, death in the ICU, in-hospital death, cessation of renal-replacement therapy, duration of ICU and hospital stays, duration of mechanical ventilation and renal-replacement therapy, dialysis status at day 90, and any new organ failures.

STATISTICAL ANALYSIS

All statistical analyses were conducted according to a predefined plan.[10,11] The target enrollment was 1500 patients, which provided 90% power to detect an 8.5% absolute reduction in 90-day mortality from a baseline of 60% (alpha level, <0.05). Two interim analyses were performed and reviewed by an independent data and safety monitoring committee. Since the Haybittle–Peto rule with a maximum of three analyses was used to limit the overall probability of a type I error to 0.05, the final analysis was conducted at an alpha level of 0.048.

All analyses were performed according to the intention-to-treat principle, with no imputation for missing values. Data from patients who were lost to follow-up were not analyzed. Proportions were compared with the use of the chi-square test,

and continuous variables were analyzed with the use of Student's t-test. Mantel–Haenszel adjusted odds ratios and their corresponding 95% confidence intervals were calculated. Analysis of the primary outcome for the two groups was also performed by means of the log-rank test, with the results presented as a Kaplan–Meier cumulative-incidence plot.

Prespecified subgroup analyses were performed according to the presence or absence of sepsis; failure of one or more nonrenal organs; a Sequential Organ Failure Assessment (SOFA) cardiovascu-

Table 1. Baseline Characteristics of the Study Patients.*

Characteristic	Higher-Intensity CRRT (N=722)†	Lower-Intensity CRRT (N=743)
Age — yr	64.7±14.5	64.4±15.3
Male sex — no. (%)	474 (65.7)	472 (63.5)
Mean preadmission eGFR — ml/min‡	54.1±32.0	58.9±29.8
Patients with known eGFR — no./total no. (%)‡		
46 to <60 ml/min	71/408 (17.4)	75/407(18.4)
30 to <46 ml/min	79/408 (19.4)	78/407 (19.2)
<30 ml/min	101/408 (24.8)	69/407 (17.0)
Time in ICU before randomization — hr	48.4±98.3	54.5±136
Mechanical ventilation — no. (%)	531 (73.5)	551 (74.2)
Severe sepsis — no. (%)	360 (49.9)	363 (48.9)
APACHE III score§	102.5±25.9	102.3±25.5
Mean SOFA score¶		
Cardiovascular	2.8±1.6	2.9±1.5
Respiratory	2.8±0.9	2.7±1.0
Coagulation	0.9±1.1	1.0±1.1
Liver	0.9±1.2	1.0±1.1
Weight — kg	80.8±12.7	80.5±13.1
Source of admission — no./total no. (%)		
Emergency department	163/670 (24.3)	185/700 (26.4)
Hospital ward	210/670 (31.3)	177/700 (25.3)
Transfer from another ICU	51/670 (7.6)	60/700 (8.6)
Transfer from another hospital	73/670 (10.9)	81/700 (11.6)
OR after emergency surgery	93/670 (13.9)	113/700 (16.1)
OR after elective surgery	80/670 (11.9)	84/700 (12.0)
Nonoperative admission diagnosis — no./total no. (%)		
Cardiovascular	268/533 (50.3)	266/516 (51.6)
Genitourinary	120/533 (22.5)	109/516 (21.1)
Respiratory	79/533 (14.8)	67/516 (13.0)
Gastrointestinal	35/533 (6.6)	40/516 (7.8)
Other	31/533 (5.8)	34/516 (6.6)
Operative admission diagnosis — no./total no. (%)		
Cardiovascular	122/189 (64.6)	147/227 (64.8)
Gastrointestinal	50/189 (26.5)	48/227 (21.1)
Trauma	6/189 (3.2)	15/227 (6.6)
Other	11/189 (5.8)	17/227 (7.5)

Table 1. (Continued.)

Characteristic	Higher-Intensity CRRT (N=722†)	Lower-Intensity CRRT (N=743)
Criteria for randomization — no./total no. (%)‖		
Oliguria (urine, <400 ml/day)	430/722 (59.6)	444/743 (59.8)
Hyperkalemia	68/722 (9.4)	45/743 (6.1)
Severe acidemia	257/722 (35.6)	264/743 (35.5)
BUN >70 mg/dl (plasma urea >25 mmol/liter)	315/722 (43.6)	286/743 (38.5)
Creatinine >3.4 mg/dl (300 μmol/liter)	349/722 (48.3)	343/743 (38.5)
Severe organ edema associated with acute kidney disease	323/722 (44.7)	319/743 (42.9)
BUN — mmol/liter**	24.2±13.3	22.8±12.2
Creatinine before randomization — μmol/liter††	338±192	330±197
pH	7.3±0.1	7.3±0.1
Bicarbonate — mmol/liter	18.1±5.7	18.5±5.9
Base excess — mmol/liter	−8.3±7	−8.2±7

* Plus–minus values are means ±SD. AKI denotes acute kidney injury, APACHE Acute Physiology and Chronic Health Evaluation, BUN blood urea nitrogen, CRRT continuous renal-replacement therapy, eGFR estimated glomerular filtration rate, ICU intensive care unit, OR operating room, and SOFA Sequential Organ Failure Assessment.
† Total includes one patient lost to follow-up.
‡ Data are for patients in whom the eGFR before randomization was known.
§ APACHE III scores range from 0 to 299, with higher scores indicating more severe illness.
¶ SOFA cardiovascular scores range from 0 to 4, with a higher score indicating more severe organ dysfunction.
‖ A given patient may have met more than one of these criteria.
** To convert the values for blood urea nitrogen to milligrams per deciliter, divide by 0.357.
†† Information on premorbid creatinine was available in 408 and 407 patients in the higher-intensity and lower-intensity groups, respectively. To convert the values for creatinine to milligrams per deciliter, divide by 88.4.

lar score of 3 or 4 at baseline (on a scale ranging from 0 to 4, with a higher score indicating more severe organ dysfunction); and an estimated glomerular filtration rate of less than 60 ml per minute within 6 months prior to randomization. We assessed subgroups for heterogeneity of treatment effect according to accepted clinical guidelines.[12]

Statistical analyses were performed, independently checked, and replicated with the use of SAS software, version 9.1.

RESULTS

ENROLLMENT

Between December 1, 2005, and August 31, 2008, we enrolled 1508 patients, of whom 747 were assigned to the higher-intensity treatment group and 761 to the lower-intensity treatment group (Fig. 1). Consent was subsequently withheld or withdrawn for 43 patients (2.9%), 25 of whom had been assigned to higher-intensity therapy and 18 to lower-intensity therapy; only 1 patient was lost to follow-up, thus the primary outcome was available for 1464 patients (97.1%).

BASELINE CHARACTERISTICS

All baseline characteristics were similar between the two groups (Table 1). The serum creatinine concentrations before randomization in the higher-intensity and lower-intensity treatment groups were 3.8 mg per deciliter (338 μmol per liter) and 3.7 mg per deciliter (330 μmol per liter), respectively. In all, 73.9% of patients were receiving mechanical ventilation, 49.4% had severe sepsis, and 82.5% were receiving vasoactive drugs.

STUDY AND SUPPORTIVE TREATMENTS

Table 2 lists the characteristics of the study therapy. The mean duration of treatment in the two groups was similar, but during therapy, they had significantly different mean daily serum creatinine concentrations (1.9 mg per deciliter [170 μmol per liter] in the higher-intensity group vs. 2.3 mg per deciliter [204 μmol per liter] in the lower-intensity group, P<0.001) and blood urea nitrogen levels (35.6 mg per deciliter [12.7 mmol per liter] vs. 44.5 mg per deciliter [15.9 mmol per liter], P<0.001). These differences were consistent with the difference in the intensity of the delivered treatment

Table 2. Characteristics of Study Treatments and Subsequent Use of Renal-Replacement Therapy.*

Characteristic	Higher-Intensity CRRT	Lower-Intensity CRRT	P Value†
Duration of study treatment — days	6.3±8.7	5.9±7.7	0.35
Flow rate of effluent — ml/kg/hr	33.4±12.8	22±17.8	<0.001
Dose delivered — %	0.84±0.27	0.88±0.34	<0.001
BUN — mmol/liter/day‡	12.7±8.5	15.9±7.9	<0.001
Serum creatinine — μmol/liter/day§	170±121	204±115	<0.001
Dialysate and replacement fluid — ml/hr	2588±1122	1666±1204	<0.001
Dose of effluent — ml/hr/day	2698±1154	1771±1257	<0.001
Net ultrafiltration — ml/hr	110±100	106±108	0.04
Fluid balance — ml/day	−20±29	−20±26	0.24
Duration of anticoagulation — days			
Prefilter heparin	2.2±3.3	2.2±3.3	0.97
No anticoagulation	1.6±2.9	1.8±2.9	0.27
Heparin and protamine	1.1±3.0	0.7±2.0	0.007
Systemic heparin	0.7±1.9	0.7±2.10	0.40
Other	0.3±1.5	0.2±1.2	0.38
Type of anticoagulant received — no./total no. (%)¶			
Prefilter heparin	348/722 (48.2)	355/743 (47.8)	0.87
No anticoagulant	332/722 (46.0)	379/743 (51.0)	0.05
Heparin and protamine	145/722 (20.1)	132/743 (17.8)	0.25
Systemic heparin	125/722 (17.3)	138/743 (18.6)	0.52
Other	48/722 (6.6)	42/743 (5.7)	0.42
Filters used daily — no.	0.93±0.86	0.84±0.81	<0.001
Patients treated with IHD in ICU — no. (%)	55/722 (7.6)	52/743 (7.0)	0.64

* Plus–minus values are means ±SD. BUN denotes blood urea nitrogen, CRRT continuous renal-replacement therapy, ICU intensive care unit, and IHD intermittent hemodialysis.
† P values were calculated with the use of Student's t-test or the chi-square test, as appropriate.
‡ To convert the values for blood urea nitrogen to milligrams per deciliter, divide by 0.357.
§ To convert the values for creatinine to milligrams per deciliter, divide by 88.4.
¶ Some patients received more than one type of anticoagulant.

(mean effluent rate, 33.4 ml per kilogram of body weight per hour in the higher-intensity group vs. 22.0 in the lower-intensity group; P<0.001). Patients receiving higher-intensity continuous renal-replacement therapy were more likely to receive regional extracorporeal-circuit anticoagulation with heparin and protamine (P=0.007) and required more filters per day (0.93 vs. 0.84, P<0.001). Only 7.6% and 7.0% of the patients in the higher-intensity and the lower-intensity groups, respectively, underwent intermittent hemodialysis at any time during their ICU stay, for a total of 314 dialysis sessions by day 28 after randomization.

TREATMENT LIMITATIONS

Among patients who died, limitations of ICU treatment were instituted for 289 of 322 patients in the higher-intensity group and 301 of 332 patients in the lower-intensity group (89.8% and 90.7%, respectively; P=0.52). Among these patients, treatment was withdrawn or limited because death was considered to be imminent in 219 of 322 patients in the higher-intensity group and in 232 of 332 patients in the lower-intensity group (68.0% and 69.9%, respectively; P=0.49). Intensive treatment was withheld, since further maximal therapy was not indicated in 70 patients (21.7%) in the

Table 3. Primary and Secondary Outcomes.*

Outcome	Higher-Intensity CRRT	Lower-Intensity CRRT	Odds Ratio	P Value†
Death — no./total no. (%)				
By day 90	322/721 (44.7)	332/743 (44.7)	1.00 (0.81–1.23)	0.99
By day 28	278/722 (38.5)	274/743 (36.9)	1.07 (0.87–1.32)	0.52
Place of death — no./total no. (%)				
ICU	251/722 (34.8)	254/743 (34.2)	1.026 (0.827–1.273)	0.81
Hospital ward	68/722 (9.4)	76/743 (10.2)	0.913 (0.647–1.288)	0.60
Outside hospital, after discharge	3/722 (0.4)	2/743 (0.3)	1.546 (0.258–9.279)	0.63
RRT dependence among survivors				
At day 28	64/443 (14.4)	57/469 (12.2)	1.22 (0.83–1.79)	0.31
At day 90	27/399 (6.8)	18/411 (4.4)	1.59 (0.86–2.92)	0.14
No. of days of RRT, from randomization to day 90	13.0±20.8	11.5±18.0	—	0.14
No. of days in ICU	11.8±14.1	11.8±14.2	—	0.95
No. of days in hospital	26±25.8	25.7±24.7	—	0.79
No. of days of mechanical ventilation	7.3±5	7.4±5	—	0.79
No. of nonrenal organ failures — no./total no. (%)‡				
0	344/722 (47.6)	343/743 (46.2)	—	0.57
1	254/722 (35.2)	263/743 (35.4)	—	0.93
2	100/722 (13.9)	109/743 (14.7)	—	0.65
3	23/722 (3.2)	25/743 (3.4)	—	0.85
4	1/722 (0.1)	3/743 (0.4)		0.33

* Plus–minus values are means ±SD.
† P values were calculated with Student's t-test or the chi-square test, as appropriate.
‡ Data on nonrenal organ failures are for the 90-day study period.

higher-intensity group and in 69 patients (20.8%) in the lower-intensity group.

PRIMARY OUTCOME

Within 90 days after randomization, death occurred in 322 (44.7%) of 721 patients in the higher-intensity group and in 332 (44.7%) of 743 patients in the lower-intensity group (odds ratio in the higher-intensity group, 1.00; 95% confidence interval [CI], 0.81 to 1.23; P=0.99) (Table 3 and Fig. 2). Mortality was also similar between the two treatment groups in all prespecified subgroups (Fig. 3).

SECONDARY AND TERTIARY OUTCOMES

There were no significant differences between the groups in any of the secondary or tertiary outcomes (Table 3). At 28 days after randomization, 64 patients (14.5% of survivors) in the higher-intensity group and 57 patients (12.2% of survivors) in the lower-intensity group were still receiving renal-replacement therapy. At 90 days, these numbers had dropped to 27 patients (6.8% of survivors) and 18 patients (4.4% of survivors), respectively (odds ratio in the higher-intensity group, 1.59; 95% CI, 0.86 to 2.92; P=0.14). Oliguria (urinary excretion, <400 ml per day) was present in 59.7% of patients at randomization.

COMPLICATIONS OF THERAPY

In the higher-intensity group, there were seven serious adverse events (three cases of the disequilibrium syndrome, one case of cerebral edema, one of rectal bleeding, one of cardiac arrest, and one of too rapid correction of hyponatremia) that were considered by the site investigators to be potentially related to treatment (Table 4). In the lower-intensity group, there were five serious adverse events (three cases of heparin-induced thrombocytopenia, one case of hypoxemia, and one of car-

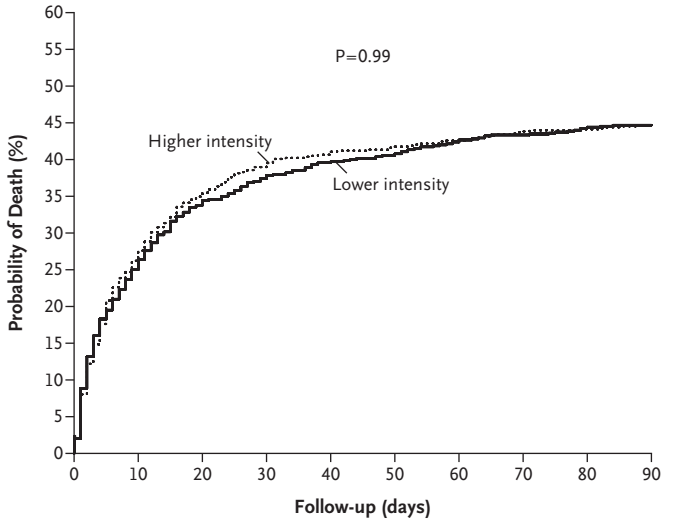

Figure 2. Kaplan–Meier Estimates of the Probability of Death.
Mortality at 28 days was similar in the higher-intensity and lower-intensity treatment groups (38.5% and 36.9%, respectively), and mortality at 90 days was the same (44.7%) in both groups.

diogenic shock). Hypophosphatemia was detected in 461 patients (65.1%) in the higher-intensity group and in 396 patients (54.0%) in the lower-intensity group (P<0.001).

DISCUSSION

In this multicenter, randomized, controlled trial of the intensity of continuous renal-replacement therapy, we found that the higher-intensity treatment did not decrease mortality as compared with the lower-intensity treatment. There were also no significant differences in the rate of recovery (i.e., cessation of dialysis because it was no longer needed) or in the occurrence of organ failure, the need for mechanical ventilation, time spent in the ICU, or time spent in the hospital.

Our findings do not agree with those of two previous randomized, controlled studies of continuous renal-replacement therapy intensity,[5,6] which showed decreased mortality with increased intensity of treatment. In a study of 425 patients, Ronco et al.[5] reported a decrease in mortality from 59 to 43% when the prescribed effluent flow was increased from 20 ml per kilogram per hour to 35 or 45 ml per kilogram per hour. In a similar study involving 206 patients, Saudan et al.[6] observed a 20% reduction in all-cause mortality at 90 days (from 61 to 41%) with an increase in the prescribed effluent flow from 25 ml per kilogram per hour to approximately 43 ml per kilogram per hour. However, the results in our study are consistent with those of two other randomized, controlled studies. Bouman et al.[7] reported no increase in survival among 106 patients in a comparison of prescribed effluent flows of 48 and 20 ml per kilogram per hour. Similarly, Tolwani et al.[8] found no difference in outcome among 200 patients randomly assigned to an effluent flow of either 20 or 35 ml per kilogram per hour.

The lower-intensity treatment in our trial was similar to that usually prescribed in ICUs in Australia and New Zealand[13] and was also identical to that prescribed for the control group in one of the trials of continuous renal-replacement therapy intensity in which the results were positive.[6] For the higher-intensity dose, we chose a value of 40 ml per kilogram per hour, which was intermediate between the two higher doses in the study by Ronco et al.[5] and similar to the higher-intensity treatment group in the study by Saudan et al.[6] In addition, the prescribed difference between treatment intensities (15 ml per kilogram per hour) in our study was identical to that prescribed in these studies.[5,6,14] Although the target doses were always achieved when continuous renal-replacement therapy was delivered, treatments were frequently interrupted owing to clotting of the filter, surgery, diagnostic investigations, or other procedures. In the Acute Renal Failure Trial Network Study,[9] the dose delivered was 89% of that prescribed for higher-intensity treatment, whereas Tolwani et al.[8] reported a value of 83% and the value in our study was 84%. For the lower-intensity treatment, the doses delivered were 95% in the Acute Renal Failure Trial Network Study as compared with 85% in the study by Tolwani et al. and 88% in our study. In all previous studies, delivered doses were less than 85% of the prescribed doses.[15-17]

Our findings are consistent with those of the Acute Renal Failure Trial Network Study,[9] which used a combination of continuous and intermittent renal-replacement therapy. In contrast to that study, however, we used continuous renal-replacement therapy exclusively — the preferred approach to renal-replacement therapy in ICUs in Australia, New Zealand, the United Kingdom, and many centers worldwide[1,18] — and ours included patients with stage 4 chronic kidney disease.[19]

Despite the similarities in primary outcome in

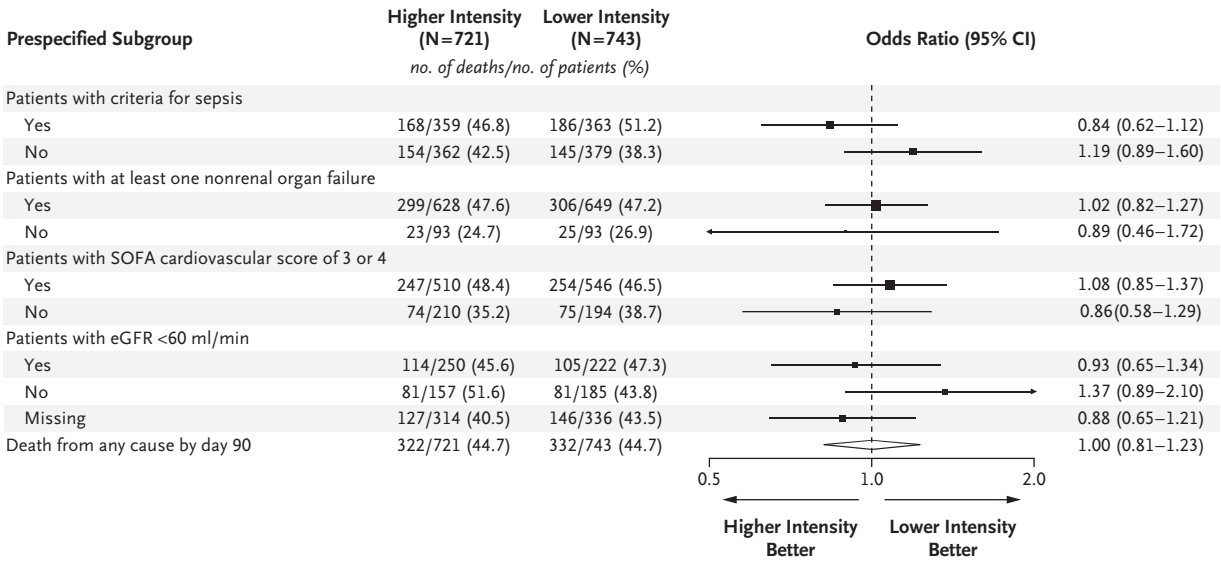

Figure 3. Mortality in the Prespecified Subgroups and among All Patients.

Odds ratios and 95% confidence intervals are shown for deaths in the four prespecified subgroups for both treatment pairs and for death from any cause by day 90 for all patients. CI denotes confidence interval, eGFR estimated glomerular filtration rate, and SOFA Sequential Organ Failure Assessment (range of scores, 0 to 4). Larger squares represent greater numbers of patients.

our study and the Acute Renal Failure Trial Network Study, there were some differences in the characteristics of the patients. Our patients were older and had a lower body weight, a lower incidence of sepsis, and higher mean scores on the cardiovascular and respiratory system SOFA. There were also differences in the processes of care. Our patients had not undergone renal-replacement therapy before randomization, whereas 64% of patients in the Acute Renal Failure Trial Network Study had undergone renal-replacement therapy in the 24 hours before randomization. In our study, the mean time from ICU admission to randomization was 50 hours, as compared with 150 hours in the other trial. Finally, our patients received only 314 intermittent hemodialysis treatments during the study therapy phase, as compared with 5077 hemodialysis treatments in the other trial. The rate of dependence on dialysis among study survivors at 28 days was 15.8% in our study as compared with 45.2% in the Acute Renal Failure Trial Network Study and 5.6% at 90 days in our study, as compared with 24.6% at 60 days in the other study.

In our efforts to achieve a high degree of internal and external validity, we ensured allocation concealment before randomization and used a primary outcome that was not subject to ascertainment bias. We enrolled 88.8% of fully eligible patients,[20] followed a predetermined statistical-analysis plan,[10] and were able to follow up on all but one patient. The management of renal-replacement therapy was designed to be in accord with standard practice in Australia and New Zealand.[12] Nearly all the patients received their assigned treatments, and there was a substantial difference in the intensity of the delivered doses of renal-replacement therapy. By including patients with preexisting stage 4 chronic kidney disease and by using continuous renal-replacement therapy (the preferred form of renal-replacement therapy in many countries and centers), we sought to increase the external validity of our results. We acknowledge, however, that a substantial number of the serum creatinine measurements within 6 months prior to randomization were unavailable (Table 1), thus limiting the conclusions that could be drawn regarding the effect of chronic kidney disease on the study outcomes.

The trial had several limitations: the study personnel and staff were aware of patients' treatment status, the timing of dialysis initiation was not standardized, and data to assess the costs of the interventions were not gathered. In addition, op-

Table 4. Summary of Complications Associated with Study Treatment.

Complication	Higher-Intensity CRRT	Lower-Intensity CRRT	P Value
Hypophosphatemia*			
No. of patients/total no.(%)	461/708 (65.1)	396/733 (54.0)	<0.0001
No. of episodes	1495	1059	—
Hypokalemia*			
No. of patients/total no. (%)	168/718 (23.4)	180/737 (24.4)	0.34
No. of episodes	297	308	0.93
Arrhythmia			
No. of patients/total no. (%)	303/722 (42.0)	337/741 (45.5)	0.18
No. of episodes	545	617	0.27
Arrhythmia requiring treatment			
No. of patients/total no. (%)	240/722 (33.2)	267/741 (36.0)	0.26
No. of episodes	388	413	0.71
Arrhythmia causing hemodynamic instability			
No. of patients/total no. (%)	200/722 (27.7)	181/741 (24.4)	0.15
No. of episodes	299	257	0.10
Disequilibrium			
No. of patients/total no. (%)	3/722 (0.4)	0/743	0.08
No. of episodes	3	0	—
One or more other serious adverse events			
No. of patients/total no. (%)	4/722 (0.6)	5/743 (0.7)	0.77
No. of episodes	4	5	—

* Levels were measured in routine morning blood samples.

erational characteristics such as frequent filter clotting could have influenced solute clearance. The difference between the prescribed dose and the delivered dose highlights the risk of overestimating the effective delivery of therapy and the need to improve operational measures in continuous renal-replacement therapy. Specifically, basing the delivered dose on effluent volume most likely overestimates true solute clearance. Future trials should measure solute clearance rather than simply relying on effluent volume. Furthermore, we cannot exclude the possibility that individual patients may benefit from personalized prescriptions. We did not use a prespecified creatinine clearance to trigger the cessation of therapy, since this was not standard practice in the study centers. Accordingly, we used cessation of renal-replacement therapy as a clinically relevant measure of the recovery of kidney function. The greater frequency of morning hypophosphatemia in the higher-intensity treatment group is consistent with the increased phosphate losses that would be expected with more intense treatment and was similarly noted in the Acute Renal Failure Trial Network Study.[9]

In countries where continuous renal-replacement therapy is now the preferred form of renal-replacement therapy in the ICU, our study has implications for clinical practice. We found that a prescribed treatment intensity that exceeds 25 ml of effluent flow per kilogram per hour adds no significant benefit and exposes patients to the risk of hypophosphatemia. There has been a widespread increase in the use of higher-intensity continuous renal-replacement therapy,[4,19] and our findings indicate that such practice is not justified. However, it must be emphasized that the dose delivered in our lower-intensity group was higher than the doses that are used in many centers.[4,15-17] Furthermore, the lower dose in our control group

was associated with a lower mortality than was reported in a large international study of the treatment of acute renal failure in critically ill patients.[4] Thus, our findings suggest not that the intensity of renal-replacement therapy is unimportant but rather that increases beyond an adequate level of intensity provide no additional benefit in critically ill patients. The results also suggest that some specific aspects of renal-replacement therapy in critically ill patients — that is, the effect of the timing of treatment initiation on mortality and the effect of continuous as compared with intermittent treatment on renal recovery — should be prioritized for investigation in future trials.

In conclusion, this large, randomized, controlled trial showed that increasing the intensity of continuous renal-replacement therapy from 25 to 40 ml of effluent flow per kilogram per hour does not reduce mortality or the rate of dependence on dialysis among critically ill patients.

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APPENDIX

The RENAL Replacement Therapy Study is a collaboration of the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG) and the George Institute for International Health. **Writing Committee:** R. Bellomo — *Austin Hospital;* A. Cass, R. Norton, M. Gallagher, S. Lo, S. Su — *George Institute for International Health;* L. Cole — *Nepean Hospital:* S. Finfer — *Royal North Shore Hospital;* C. McArthur, S. McGuinness — *Auckland City Hospital;* J. Myburgh — *St. George Hospital (Sydney);* C. Scheinkestel — *Alfred Hospital.* **Management Committee:** R. Bellomo (chair), J. Lee (senior project manager), D. Ali, A. Cass, L. Cole, S. Finfer, M. Gallagher, D. Goldsmith, S. McGuinness, J. Myburgh, R. Norton, C. Scheinkestel. **Steering Committee:** R. Bellomo (chair), A. Banerjee, D. Bhonagiri, D. Blythe, J. Botha, J. Cade, L. Cole, G. Dobb, J. Eddington, S. Finfer, A. Flabouris, C. French, P. Garrett, S. Henderson, B. Ihle, C. Joyce, M. Kalkoff, J. Lipman, C. McArthur, S. McGuinness, D. Milliss, I. Mitchell, J. Morgan, J. Myburgh, P. Nair, N. Orford, A. Raza, C. Scheinkestel, Y. Shehabi, A. Tobin, R. Totaro, A. Turner, C. Wright. **Project Management Team:** D. Ali, J. Lee, L. Little, A. Morrison, G. Regaglia, R. Shukla. **Data Safety and Monitoring Committee:** C. Baigent (chair), J. Emberson, D. Wheeler, D. Young. **Statistics Committee:** L. Billot, S. Bompoint, S. Heritier, S.N. Lo, A. Pillai, S. Su. **Data Management and Information Technology/Programming:** S. Pandey, S. Ryan, M. Schmidt, G. Starzec, B. Vijayan. **Site Investigators and Research Coordinators:** *Australian Capital Territory — Canberra Hospital:* I. Mitchell, R. Ashley, J. Gissane, K. Malchukova, J. Ranse. *New South Wales — Blacktown Hospital:* A. Raza, K. Nand, T. Sara; *Concord Hospital:* W. Cheung, E. Fugaccia, P. Lawrence, D. Millis, J. Tan, G. Thankrishnan, H. Wong; *John Hunter Hospital:* P. Harrigan, E. Crowfoot, M. Hardie; *Liverpool Hospital:* D. Bhonagiri, S. Micallef; *Newcastle — Mater Calvary Hospital:* J. Brieva, M. Lintott; *Nepean Hospital:* L. Cole, I. Seppelt, R. Gresham, M. Nikas, L. Weisbrodt; *Prince of Wales Hospital:* Y. Shehabi, F. Bass, M. Boyle, M. Campbell, N. Hammond. *Victoria — Stockdale Royal North Shore Hospital:* S. Finfer, S. Ankers, A. O'Connor, Julie Potter; *Royal Prince Alfred Hospital:* R. Totaro, D. Rajbhandari; *St. George Hospital:* J. Myburgh, V. Dhiacou, A. Jovanovska, F. Munster; *St. Vincent's Hospital:* P. Nair, J. Breeding, C. Burns; *Westmead Hospital:* A. Banerjee, M. Morrison, C. Pfeffercorn, A. Ritchie. *New Zealand — Auckland City Hospital/Cardiovascular Intensive Care Unit:* S. McGuinness, H. Buhr, M. Eccleston, R. Parke; *Auckland City Hospital/Department of Critical Care Medicine:* C. McArthur, J. Bell, L. Newby; *Christchurch Hospital:* S. Henderson, J. Mehrtens; *Whangarei Hospital:* M. Kalkoff, C. West. *Queensland — Mater Adult and Mater Private Hospital:* J. Morgan, L. Rudder, J. Sutton; *Nambour General Hospital:* P. Garrett, N. Groves, S. McDonald, J. Jaspers; *Princess Alexandra Hospital:* C. Joyce, M. Harwood, J. Helyar, B. Mackie; *Royal Brisbane Hospital:* J. Lipman, R. Boots, C. Bertenshaw, R. Deans, C. Fourie, M. Lassig-Smith, J. Stuart. *South Australia — Royal Adelaide Hospital:* A. Flabouris, J. Edwards, S. O'Connor, K. Lewis, J. Rivett. *Tasmania — Royal Hobart Hospital:* A. Turner, T. Field, R. McAllister, K. Marsden. *Victoria — Austin Hospital:* R. Bellomo, C. Mathlin, D. Goldsmith, I. Mercer, K. O'Sullivan; *Bendigo Hospital:* J. Edington, C. Boschert, J. Smith; *Epworth Hospital:* B. Ihle, M. Graan, S. Ho; *Frankston Hospital:* J. Botha, N. Fowler, J. McInness, N. Pratt; *Geelong Hospital:* N. Orford, T. Elderkin, M. Fraser, A. Kinmonth; *Monash Medical Centre:* C. Wright, J. Barrett, S. Wilson, P. Galt, S. Burton, C. Culhane, R. Ioannidis; *Royal Melbourne Hospital:* M. Roberston, D. Barge, T. Caf, B. Howe, P. Low; *St. Vincent's Hospital Melbourne:* A. Tobin, N. Groves, J. Holmes, R. Smith; *Alfred Hospital:* C. Scheinkestel, A. Davies, L. Murray, R. Nevill, S. Vallance, S. Varley, V. White; *Western Hospital:* C. French, L. Little, H. Raunow. *Western Australia — Fremantle Hospital:* D. Blythe, A. Palermo; *Royal Perth Hospital:* G. Dobb, M. Boardman, J. Chamberlain, A. Gould, G. McEntaggart, S. Perryman, L. Thomas.

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