EDITORIALS

Renal Support in Acute Kidney Injury — How Much Is Enough?

Paul M. Palevsky, M.D.

Decrements in kidney function occur in more than two thirds of hospitalized patients with critical illness,[1] and severe acute kidney injury complicates the care of more than 5% of patients who require intensive care.[2] Despite the potential for recovery of kidney function, acute kidney injury is associated with substantial morbidity. Mortality rates among critically ill patients with acute kidney injury range from 30% to more than 60%.[2-6] In the absence of effective pharmacologic therapy, the care of patients with acute kidney injury is predominantly supportive: optimizing hemodynamic and volume status, correcting electrolyte and acid–base disturbances, providing adequate nutrition, and adjusting drug doses. In patients with sustained, severe renal failure, dialysis, hemofiltration, and other forms of renal-replacement therapy are instituted with the goal of restoring a normal homeostatic milieu while awaiting the recovery of kidney function. Although more than 60 years have passed since the first successful clinical application of dialysis in patients with acute kidney injury, fundamental management issues remain controversial, including when to start dialytic therapy and what constitutes the appropriate dose.

The intensity of renal-replacement therapy can be described in terms of multiple factors, including fluid balance and clearance of high-molecular-weight plasma constituents. However, renal-replacement therapy is most commonly quantified in terms of urea kinetics, with urea serving as a surrogate for the clearance of other low-molecular-weight solutes. In intermittent forms of dialysis, the dose depends on both the frequency of the dialysis sessions and the clearance achieved during each individual treatment; the latter variable can be modified by altering the dialyzer, varying the rates of blood flow and dialysate flow, or changing the duration of treatment. In contrast, when continuous forms of renal-replacement therapy are used, urea clearance varies in proportion to the combined rates of dialysate flow and ultrafiltrate flow. The issue of the intensity of renal-replacement therapy is not inconsequential. Although an increased intensity of therapy restores a more physiologic plasma composition, thus counterbalancing the increased catabolic state associated with acute kidney injury, this higher intensity is associated with an increased risk of iatrogenic electrolyte disturbances such as hypophosphatemia and hypokalemia,[5] micronutrient depletion, subtherapeutic doses of antibiotics and other drugs, and dialysis-associated hypotension.[5] Furthermore, an increased intensity of therapy is associated with increased costs.

Over the past decade, the results of several single-center trials have suggested that increasing the intensity of renal-replacement therapy may improve survival among critically ill patients with acute kidney injury[3,7,8]; however, other studies have not confirmed this benefit.[4-6] In this issue of the *Journal*, Bellomo and colleagues present the results of the Randomized Evaluation of Normal versus Augmented Level (RENAL) Replacement Therapy Study (ClinicalTrials.gov number, NCT00221013), which was conducted at multiple centers in Australia and New Zealand.[9] In the RENAL Study, 1508 patients with severe acute kidney injury who required intensive care were randomly assigned to receive continuous venovenous hemodiafiltration at a total effluent flow rate of either 25 ml or 40 ml per kilogram of

body weight per hour. The study therapy was continued until the recovery of kidney function or the patient's condition was stable enough to warrant discharge from intensive care. Consent was subsequently withheld or withdrawn for 43 patients, and 1 patient was lost to follow-up, allowing an assessment of outcomes in 1464 patients. In both treatment groups, 44.7% of patients died in the first 90 days after randomization (odds ratio, 1.00; 95% confidence interval, 0.81 to 1.23). Overall, 94.4% of patients who were alive after 90 days no longer required dialysis, with similar rates of recovery of kidney function in both treatment groups.

The results of the RENAL Study are qualitatively similar to those of the Veterans Affairs/National Institutes of Health Acute Renal Failure Trial Network Study (ClinicalTrials.gov number, NCT00076219),[5] the only previous large, multicenter, randomized, controlled trial of intensity of renal support in acute kidney injury. However, these two studies differ in several important ways. In the Acute Renal Failure Trial Network Study, continuous venovenous hemodiafiltration was used only in hemodynamically unstable patients; those who were hemodynamically stable received intermittent hemodialysis. In addition, the protocol-specified therapy was continued for up to 28 days, regardless of whether the patient remained in intensive care. In contrast, the RENAL Study used only continuous venovenous hemodiafiltration, and the study therapy was discontinued in dialysis-dependent patients when they left the intensive care unit. As a result, although only a small percentage of patients received intermittent hemodialysis while in intensive care, the mean duration of renal-replacement therapy was substantially greater than that of the actual study therapy, suggesting that a considerable amount of nonprotocol hemodialysis took place after transfer out of intensive care. The doses used in these nonstudy treatments and the associated rates of complications are not described. Overall, the mortality rates were lower and recovery of kidney function in surviving patients was more common in the RENAL Study than in the Acute Renal Failure Trial Network Study. Although it is possible that these differences are related to alternative strategies for the timing of the initiation of renal-replacement therapy and to greater use of continuous therapy, as compared with intermittent therapy, as the initial mode of renal-replacement therapy in the RENAL Study, they seem more likely to be due to differences between the two study populations.

Failure to demonstrate improved outcomes with more intensive renal-replacement therapy in critically ill patients with acute kidney injury in both the RENAL Study and the Acute Renal Failure Trial Network Study does not imply that the intensity of renal-replacement therapy does not matter. There is ample evidence of a relationship between the intensity of such therapy and outcomes.[3,7,10] The results of both these studies do imply, however, that while a threshold dose of therapy must be achieved to optimize clinical outcomes, increasing the intensity of therapy beyond this dose does not provide further clinical benefit. Thus, it is critical to attain this minimal dosing threshold. Unfortunately, this is often not the case. In fact, the delivered dose of dialysis for acute kidney injury is frequently not even assessed,[11] highlighting a need to apply the tools of quality assurance and performance improvement that are routine in outpatient dialysis to the practice of renal-replacement therapy for acute kidney injury. Adopting such tools will ensure that we provide treatment that is at least as intensive as that provided in the lower-intensity groups in these two studies. Furthermore, it should not be forgotten that patient care needs to be individualized — more intensive therapy may be required for the treatment of hyperkalemia, metabolic acidosis, or extreme hypercatabolism — and that the true adequacy of renal-replacement therapy is defined by more than just the clearance of small solutes.

Dr. Palevsky reports receiving consulting fees from Nephrion and research support from Spectral Diagnostics. No other potential conflict of interest relevant to this article was reported.

From the Renal Section, VA Pittsburgh Healthcare System; and the Renal-Electrolyte Division, Department of Medicine, University of Pittsburgh School of Medicine — both in Pittsburgh.

1. Hoste EA, Clermont G, Kersten A, et al. RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis. Crit Care 2006;10:R73.
2. Uchino S, Kellum JA, Bellomo R, et al. Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA 2005;294:813-8.
3. Ronco C, Bellomo R, Homel P, et al. Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomised trial. Lancet 2000;356:26-30.
4. Bouman CS, Oudemans-Van Straaten HM, Tijssen JG, Zandstra DF, Kesecioglu J. Effects of early high-volume continuous

venovenous hemofiltration on survival and recovery of renal function in intensive care patients with acute renal failure: a prospective, randomized trial. Crit Care Med 2002;30:2205-11.
5. Palevsky PM, Zhang JH, O'Connor TZ, et al. Intensity of renal support in critically ill patients with acute kidney injury. N Engl J Med 2008;359:7-20.
6. Tolwani AJ, Campbell RC, Stofan BS, Lai KR, Oster RA, Wille KM. Standard versus high-dose CVVHDF for ICU-related acute renal failure. J Am Soc Nephrol 2008;19:1233-8.
7. Schiffl H, Lang SM, Fischer R. Daily hemodialysis and the outcome of acute renal failure. N Engl J Med 2002;346:305-10.
8. Saudan P, Niederberger M, De Seigneux S, et al. Adding a dialysis dose to continuous hemofiltration increases survival in patients with acute renal failure. Kidney Int 2006;70:1312-7.
9. The RENAL Replacement Therapy Study Investigators. Intensity of continuous renal-replacement therapy in critically ill patients. N Engl J Med 2009;361:1627-38.
10. Paganini EP, Tapolyai M, Goormastic M, et al. Establishing a dialysis therapy/patient outcome link in intensive care unit acute dialysis for patients with acute renal failure. Am J Kidney Dis 1996;28:S81-S89.
11. Overberger P, Pesacreta M, Palevsky PM. Management of renal replacement therapy in acute kidney injury: a survey of practitioner prescribing practices. Clin J Am Soc Nephrol 2007;2:623-30.

Blood-Pressure Control and Delay in Progression of Kidney Disease in Children

Julie R. Ingelfinger, M.D.

Many children with chronic kidney disease, even those in whom the disease is discovered very early, ultimately lose renal function; some ultimately progress to stage 5 chronic kidney disease (end-stage renal disease). Causes of chronic kidney disease in children differ substantially from those in adults; the largest diagnostic categories in children are congenital renal and genitourinary abnormalities; obstructive uropathy or renal hypoplasia–dysplasia are most common, followed by reflux nephropathy and focal segmental glomerulosclerosis.[1,2]

Despite much evidence that blocking the renin–angiotensin system is helpful in treating adults with various nephropathies,[3] comparable data from randomized, controlled trials involving children are lacking. Although case reports, case series, and nonrandomized trials have been published, randomized studies examining potential renoprotection in children have been much awaited. More than 20 years ago, Trachtman and Gauthier reported that angiotensin-converting–enzyme (ACE) inhibition decreased proteinuria in eight children with chronic kidney disease.[4] Subsequently, Lama et al.[5] reported a decrease in proteinuria and a slowing of the progression of renal disease with ACE-inhibitor therapy in a small 2-year observational study. More recently, a case–control study from the Italian Pediatric Registry of Chronic Renal Insufficiency (the ItalKid Project), a database of children with glomerular filtration rates less than 90 ml per minute per 1.73 m^2 of body-surface area, concluded that the evidence that ACE inhibition was effective in halting the progression of chronic kidney disease in children with the most common form of pediatric renal disease — hypoplasia or dysplasia — was unclear.[6] However, finding sufficient patients to study in pediatric trials, including in the ItalKid Project, is difficult; of 162 patients with chronic renal insufficiency due to renal hypoplasia or dysplasia in the registry, only 41 were available for study after children younger than 2 years of age, those with less than 2 years of follow-up, and those with fewer than three data points were excluded. Thus, prospective trials examining the effects of treatment in preventing progression have been awaited.

In this issue of the *Journal,* the results of a 5-year randomized trial, the Effect of Strict Blood Pressure Control and ACE Inhibition on the Progression of CRF in Pediatric Patients trial (ESCAPE; ClinicalTrials.gov number, NCT00221845),[7] show that intensified blood-pressure control in children 3 to 18 years of age with chronic kidney disease (glomerular filtration rates of 15 to 80 ml per minute) who received fixed high-dose ACE inhibition consisting of ramipril at a daily dose of 6 mg per square meter offers an advantage. After a 6-month run-in period, during which any ACE inhibitor or other blocker of the renin–angiotensin system was withdrawn at least 2 months before the active phase of the study, participants were randomly assigned to intensified blood-pressure control (24-hour mean arterial pressure below the 50th percentile for age) or conventional blood-pressure control (mean arterial pressure in the 50th to 95th percentile). To achieve the tar-

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 22, 2009 VOL. 361 NO. 17

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.

N Engl J Med 2009;361:1627-38.

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-

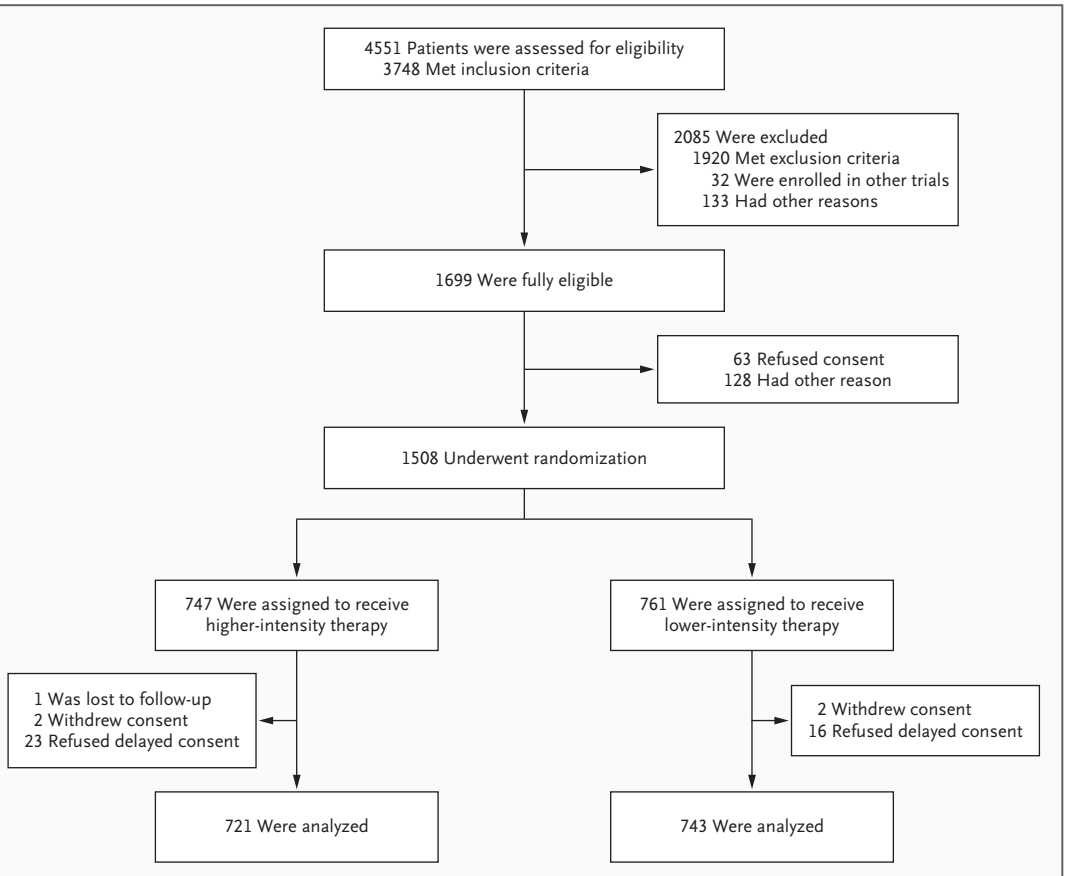

Figure 1. Numbers of Patients Enrolled in the Study, Randomly Assigned to a Treatment Group, and Included in the Analysis.

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-

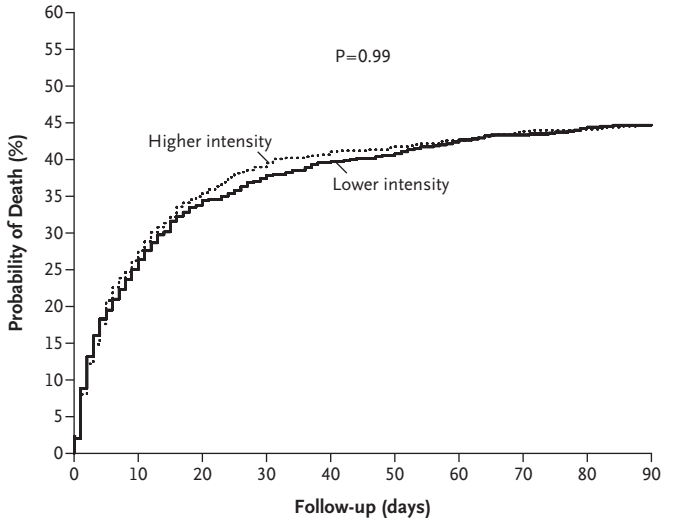

Figure 2. Kaplan–Meier Estimates of the Probability of Death.
Mortality at 28 days was similar in the higher-intensity and lower-intensity treatment groups (38.5% and 36.9%, respectively), and mortality at 90 days was the same (44.7%) in both groups.

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

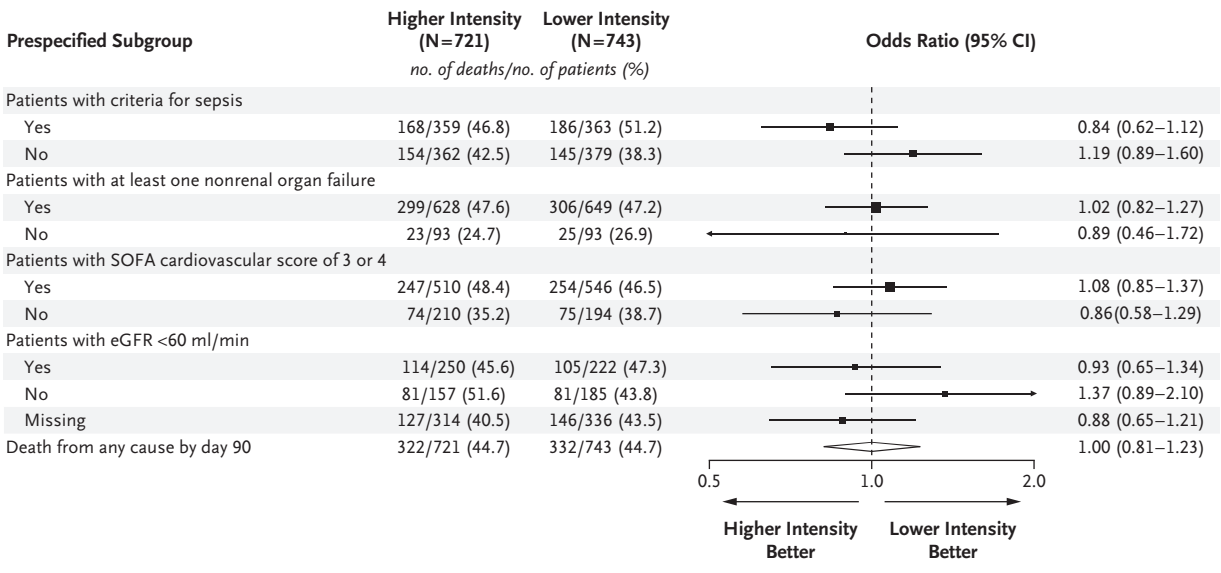

Figure 3. Mortality in the Prespecified Subgroups and among All Patients.

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.

Supported by grants from the National Health and Medical Research Council of Australia (352550) and the Health Research Council of New Zealand (06-357).

Dr. Bellomo reports receiving consulting fees from Gambro Biosite, Abbott Diagnostics, and Philips Medical Systems, and grant support from Fresenius Kabi, Bard, Pfizer, and Gambro; Dr. Cass, grant support from Fresenius Kabi, Roche, and Gambro; Dr. Finfer, travel support to present research results at scientific meetings from Eli Lilly, Cardinal Health, and CSL Bioplasma; Dr. Gallagher, lecture fees from Roche and Amgen; Dr. McArthur, grant support from Bard, Pfizer, and Gambro; and Dr. Myburgh, grant support from Fresenius Kabi. The George Institute for International Health, an independent not-for-profit institute affiliated with the University of Sydney, has received reimbursement for Dr. Finfer's time as a steering-committee member for studies sponsored by Eli Lilly and Eisai and has received research funding from Servier, Novartis, Eisai, Merck Sharp & Dohme, Pfizer Australia, Fresenius Kabi Deutschland, and Sanofi-Aventis. No other potential conflict of interest relevant to this article was reported.

We thank Gambro for providing Hemosol dialysate and replacement fluids at a favorable price; the nurses in our intensive care units, our physician colleagues, and our patients and their families; Professor Carol Pollock and Professor Peter Kerr for their assistance with protocol development; and Dr. Peter Stow for his assistance with the Acute Physiology and Chronic Health Evaluation (APACHE III) software application.

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.

REFERENCES

1. Bagshaw SM, George C, Bellomo R. Changes in the incidence and outcome for early acute kidney injury in a cohort of Australian intensive care units. Crit Care 2007;11:R68.

2. Hoste EA, Clermont G, Kersten A, et al. RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis. Crit Care 2006;10:R73.

3. Uchino S, Bellomo R, Goldsmith D, Bates S, Ronco C. An assessment of the RIFLE criteria for acute renal failure in hospitalized patients. Crit Care Med 2006; 34:1913-7.

4. Uchino S, Kellum JA, Bellomo R, et al. Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA 2005;294:813-8.
5. Ronco C, Bellomo R, Homel P, et al. Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomized trial. Lancet 2000;355:26-30.
6. Saudan P, Niederberger M, De Siegneux S, et al. Adding a dialysis dose to continuous hemofiltration increases survival in patients with acute renal failure. Kidney Int 2006;70:1312-7.
7. Bouman CS, Oudemans-Van Straaten HM, Tijssen JG, Zandstra DF, Kesecioglu J. Effects of early high-volume continuous venovenous hemofiltration on survival and recovery of renal function in intensive care patients with acute renal failure: a prospective, randomized trial. Crit Care Med 2002;30:2205-11.
8. Tolwani AJ, Campbell RC, Stofan BS, Lai KR, Oster RA, Wille KM. Standard versus high-dose CVVHDF for ICU-related acute renal failure. J Am Soc Nephrol 2008; 19:1233-8.
9. Palevsky PM, Zhang JH, O'Connor TZ, et al. Intensity of renal support in critically ill patients with acute kidney injury. N Engl J Med 2008;359:7-20.
10. Finfer S, Cass A, Gallagher M, Lee J, Su S, Bellomo R. The RENAL (Randomized Evaluation of Normal vs. Augmented Level Replacement Therapy) study: statistical analysis plan. Crit Care Resusc 2009;11: 58-66.
11. Finfer S, Bellomo R. Why publish statistical analysis plans? Crit Care Resusc 2009;11:5-6.
12. Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM. Statistics in medicine — reporting of subgroup analyses in clinical trials. N Engl J Med 2007;357:2189-94.
13. RENAL Study Investigators. Renal replacement therapy for acute kidney injury in Australian and New Zealand intensive care units: a practice survey. Crit Care Resusc 2008;10:225-30.
14. *Idem.* Design and challenges of the Randomized Evaluation of Normal vs. Augmented Level Replacement Therapy (RENAL) Trial: high dose vs. standard dose hemofiltration in acute renal failure. Blood Purif 2008;26:407-16.
15. Venkataraman R, Kellum JA, Palevsky P. Dosing patterns for continuous renal replacement therapy at a large academic medical center in the United States. J Crit Care 2002;17:246-50.
16. Uchino S, Fealy N, Baldwin I, Morimatsu H, Bellomo R. Continuous is not continuous: the incidence and impact of circuit "down-time" on uraemic control during continuous veno-venous haemofiltration. Intensive Care Med 2003;29:575-8.
17. Mehta RL, McDonald B, Gabbai FB, et al. A randomized clinical trial of continuous versus intermittent dialysis for acute renal failure. Kidney Int 2001;60:1154-63.
18. Gatward JJ, Gibbon GJ, Wrathall G, Padkin A. Renal replacement therapy for acute renal failure: a survey of practice in adult intensive care units in the United Kingdom. Anaesthesia 2008;63:959-66.
19. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002;39:Suppl 1:S1-S266.
20. RENAL Replacement Therapy Trial Investigators. Screening and study enrollment in the Randomized Evaluation of Normal vs. Augmented Level (RENAL) Replacement Therapy Trial. Blood Purif 2009;27:199-205.

ICMJE SEEKING TWO NEW MEMBER JOURNALS

The International Committee of Medical Journal Editors (ICMJE) is seeking two new member journals to be represented by their editors-in-chief. Information about the ICMJE is available at www.icmje.org. Given the small number of applicants and the ICMJE's recent awareness that many journals interested in applying had not seen the initial announcement posted in late June, the ICMJE has decided to extend the deadline for applications to November 30, 2009. Candidate journals should meet the following criteria:

- peer reviewed, general medical journal
- represent geographic areas (Latin America, Asia, Africa) or publication models (open access) not well represented by current ICMJE members
- editor who is knowledgeable about publication ethics
- editor who expects to be in the position for at least 3 years

To apply, editors-in-chief of interested journals should send electronic copies of the following to the ICMJE secretariat (Christine Laine at claine@acponline.org) by November 30, 2009:

- brief curriculum vitae
- description of journal, including age, sponsor/publisher, publishing model (subscription model, author pays, open access, etc.), target audience, circulation, number of manuscript submissions per year, description of peer review process used to select material for publication, acceptance rate, bibliographical databases where indexed, Web site address if applicable, and copy of guidelines for authors
- statement on why the journal/editor-in-chief wants to be an ICMJE member (should not exceed 1000 words in length)
- contact information

CORRESPONDENCE

Intensity of Continuous Renal-Replacement Therapy

TO THE EDITOR: In the Randomized Evaluation of Normal versus Augmented Level (RENAL) Replacement Therapy Study (Oct. 22 issue),[1] investigators compared low-intensity versus high-intensity renal-replacement therapy. One of the secondary outcomes was the development of new organ failure. However, the criteria for "nonrenal organ failure" were not provided.

Second, in subgroup analyses, the RENAL study showed that there was no mortality benefit with high-intensity treatment in patients with sepsis, cardiovascular dysfunction, or failure of at least one nonrenal organ. In a study involving 1847 critically ill patients receiving renal-replacement therapy, we recently reported that the number of failed organ systems at the time of such therapy had a significant effect on the rate of death in the intensive care unit, ranging from 38% in patients with one organ failure to 85.6% in patients with more than three failed organ systems.[2]

The RENAL study was not designed to perform subgroup analyses in patients with three or more associated failed organ systems. The question remains whether renal-replacement therapy should be individualized in patients with acute kidney injury and multiorgan failure and whether there is a role for high-intensity renal-replacement therapy in this group.

Marlies Ostermann, Ph.D., M.D.
Guy's and St. Thomas National Health Service Foundation Trust
London, United Kingdom
marlies@ostermann.freeserve.co.uk

Rene W. Chang, M.S.
St. George's University Hospital
London, United Kingdom

No potential conflict of interest relevant to this letter was reported.

1. The RENAL Replacement Therapy Study Investigators. Intensity of continuous renal-replacement therapy in critically ill patients. N Engl J Med 2009;361:1627-38.
2. Ostermann M, Chang RWS. Correlation between parameters at initiation of renal replacement therapy and outcome in patients with acute kidney injury. Crit Care 2009;13:R175.

TO THE EDITOR: The RENAL study on the intensity of continuous renal-replacement therapy in critically ill patients joins the study by the Veterans Affairs/National Institutes of Health Acute Renal Failure Trial Network[1] in clarifying a controversial and important issue. However, we feel that there is a risk of a change in practice that could lead to the undertreatment of patients as a consequence. First, the delivered dose of renal-replacement therapy is commonly lower than the prescribed dose in a range lower than that reported in this study. Second, the most widely used method of renal-replacement therapy is continuous venovenous hemofiltration, which was the method used by 52% of practitioners in a recent worldwide survey.[2] The absence of additional doses of dialysis added to hemofiltration may lead to

THIS WEEK'S LETTERS

undertreatment that could have an adverse effect on the outcome.[3] The use of predilution, which remains a prevalent practice of delivery of replacement solution,[4] further decreases the efficacy of the treatment. We urge intensivists not to lower treatment doses before careful evaluation of their practices for renal-replacement therapy.

Matthieu Legrand, M.D.
Didier Payen, M.D., Ph.D.
Lariboisière Hospital
Paris, France
m.legrand@libertysurf.fr

No potential conflict of interest relevant to this letter was reported.

1. The VA/NIH Acute Renal Failure Trial Network. Intensity of renal support in critically ill patients with acute kidney injury. N Engl J Med 2008;359:7-20. [Erratum, N Engl J Med 2009;361:2391.]
2. Uchino S, Bellomo R, Morimatsu H, et al. Continuous renal replacement therapy: a worldwide practice survey. Intensive Care Med 2007;33:1563-70.
3. Saudan P, Niederberger M, De Seigneux S, et al. Adding a dialysis dose to continuous hemofiltration increases survival in patients with acute renal failure. Kidney Int 2006;70:1312-7.
4. Ricci Z, Ronco C, D'Amico G, et al. Practice patterns in the management of acute renal failure in the critically ill patient: an international survey. Nephrol Dial Transplant 2006;21:690-6.

TO THE EDITOR: The RENAL study investigators conclude that high-intensity continuous renal-replacement therapy in critically ill patients with acute kidney injury had no significant effect on mortality at 90 days. In hemofiltration, solute removal works by convection. A randomized study identified a benefit of a postdilution ultrafiltration rate of more than 35 ml per kilogram of body weight per hour, as compared with 25 ml per kilogram per hour, on mortality.[1] In another study, a decreased rate of death was also reported by adding a small dose of diffusion to ultrafiltration at a rate of 25 ml per kilogram per hour.[2] The benefit of combining diffusion and convection in hemodiafiltration and the proportion of dialysate flow required remain unknown.

In the RENAL study, diffusion and convection were used simultaneously. It would be of great interest to know what doses of dialysate and ultrafiltration were delivered in each study group. As compared with previous studies,[1,2] most patients with severe sepsis would have benefited from higher ultrafiltration rates.[1] The postdilution ultrafiltration difference between low-intensity and high-intensity therapy may be insufficient. Another study design with an elicited postfilter solute-removal strategy during continuous renal-replacement therapy, with or without additional diffusion, might give different results.

Damien du Cheyron, M.D., Ph.D.
Jean-Jacques Parienti, M.D., D.T.M.&H.
Caen University Hospital
Caen, France
ducheyron-d@chu-caen.fr

No potential conflict of interest relevant to this letter was reported.

1. Ronco C, Bellomo R, Homel P, et al. Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomised trial. Lancet 2000;356:26-30.
2. Saudan P, Niederberger M, De Seigneux S, et al. Adding a dialysis dose to continuous hemofiltration increases survival in patients with acute renal failure. Kidney Int 2006;70:1312-7.

THE AUTHORS REPLY: In response to Ostermann and Chang: we assessed organ dysfunction using the Sequential Organ Failure Assessment (SOFA) score, and the presence of organ failure was identified with the use of the same system (as shown in Table 1 of our article). We agree that severity of illness predicts subsequent mortality; however, there was no evidence from our study that subgroups of sicker patients (as shown in Fig. 3 of our article) responded to the intensity of renal-replacement therapy in a different way.

Legrand and Payen are correct in stating that the intensity of delivered renal-replacement therapy is frequently less than that prescribed (as shown in our study) and that clinicians should take this factor into account in their prescription of dose.

In response to du Cheyron and Parienti: we describe the intervention, where we state that study therapy combined dialysate and replacement fluid in a 1:1 ratio so that the subsequent effluent represented a combination of close to 50% diffusive and 50% convective clearance.[1,2] It is theoretically possible that a study using analogous doses of effluent and only convective clearance might have shown a different outcome. However, the lack of any outcome difference in our study, despite differences in convective clearance, leads us to conclude that such an outcome is unlikely. We note that the only randomized, controlled study that has supported the view that renal-replacement therapy at a higher convective dose (at 35 or 45 ml per kilogram per hour) leads to a better outcome was a single-center study that has not been replicated elsewhere, used an atypical primary outcome, did not apply a predefined

statistical analysis plan,[3] and has been indirectly contradicted by two large, multicenter trials.[4]

Rinaldo Bellomo, M.D.
Austin Hospital
Melbourne, VIC, Australia
ctg@anzics.com.au

Alan Cass, M.D., Ph.D.
Martin P. Gallagher, M.D.
George Institute for International Health
Sydney, NSW, Australia

Since publication of their article, the authors report no further potential conflict of interest.

1. The RENAL Study Investigators. Renal replacement therapy for acute kidney injury in Australian and New Zealand intensive care units: a practice survey. Crit Care Resusc 2008;10:225-30.
2. *Idem.* Design and challenges of the Randomized Evaluation of Normal vs. Augmented Level Renal Replacement Therapy (RENAL) Trial: high-dose vs. standard-dose hemofiltration in acute renal failure. Blood Purif 2008;26:407-16.
3. Finfer S, Cass A, Gallagher M, Lee J, Su S, Bellomo R. The RENAL (Randomised Evaluation of Normal vs. Augmented Level Replacement Therapy) study: statistical analysis plan. Crit Care Resusc 2009;11:58-66.
4. Bellomo R, Warrillow SJ, Reade MC. Why we should be wary of single center-trials. Crit Care Med 2009;37:3114-9.

Functional Status of Elderly Adults Receiving Dialysis

TO THE EDITOR: Frail elderly patients with end-stage renal disease (ESRD) entering dialysis programs have a substantial and sustained decline in functional status, according to the article by Kurella Tamura et al.[1] and the letter by Jassal et al.[2] (Oct. 15 issue). In the accompanying editorial, Arnold and Zeidel[3] point to a lack of randomized trials to evaluate the benefit of dialysis in this group. The key difficulty in interpreting comparative survival data is uncertainty surrounding when dialysis would have started in conservatively treated patients. We used regression analysis of measurements of the estimated glomerular filtration rate to calculate an equivalent putative dialysis start date for a group of patients with ESRD who were over 70 years of age and who were treated conservatively and compared their survival with a similar group that underwent dialysis.[4] Both groups had similar scores on the Charlson Comorbidity Index, even though the conservatively treated group was older (mean age, 81.6 years vs. 76.4 years). Patients who opted for dialysis had improved survival (median, 37.8 months vs. 13.9 months), but almost every additional day of increased survival was at the expense of a hospital visit or intervention. Patients who were undergoing dialysis were more likely to die in an acute hospital setting (odds ratio, 4.15).

Aine Burns, M.D.
Andrew Davenport, M.D.
Royal Free National Health Service Trust
London, United Kingdom
aine.burns@royalfree.nhs.uk

No potential conflict of interest relevant to this letter was reported.

1. Kurella Tamura M, Covinsky K, Chertow G, Yaffe K, Landefeld C, McCulloch C. Functional status of elderly adults before and after initiation of dialysis. N Engl J Med 2009;361:1539-47.
2. Jassal SV, Chiu E, Hladunewich M. Loss of independence in patients starting dialysis at 80 years of age or older. N Engl J Med 2009;361:1612-3.
3. Arnold RM, Zeidel ML. Dialysis in frail elders — a role for palliative care. N Engl J Med 2009;361:1597-8.
4. Carson R, Juszczak M, Davenport A, Burns A. Is conservative management an equivalent option to dialysis for elderly patients with significant comorbid disease? Clin J Am Soc Nephrol 2009;4:1611-9.

TO THE EDITOR: Kurella Tamura et al. ask, "Why does functional status decline in so many nursing home residents despite the treatment of uremia?" The investigators' answers to this question missed a most relevant point: in a nursing home, brain alterations dominate the clinical picture and explain much of the functional decline. Not only are hemodialysis sessions started in parallel with cognitive fluctuation caused by the uremic state, but further cognitive instability derives from huge, uncontrollable hemodynamic and metabolic changes in the brain during hemodialysis sessions. Hypotension, hypertension, hypoxemia, electrolyte disorders, dialysis disequilibrium, accumulation of drugs (and of anticholinergic effects), vitamin deficiencies, and depression contribute to cognitive fluctuations. In the elderly, these phenomena assume extraordinary significance, and hemodialysis sessions constantly generate delirium and other acute cognitive disorders[1] that may coalesce in subsequent sessions. Williams et al.[2] detected