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The Randomized Evaluation of Normal versus Augmented Level (RENAL) Replacement Therapy Trial

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Copyright notices

Notice 1

Notice 2

Dedication

I lovingly dedicate this thesis to my wife Debbie who for more than thirty years has provided support and understanding for my, at times unreasonable, commitment to excellence and to the generation of high level evidence to guide the practice of Medicine.

I also lovingly dedicate this thesis to my daughter Hilary. May she long continue to understand and remember that the quality of a person's life is in direct proportion to their commitment to excellence.

Abstract

Approximately 5% of patients admitted to ICU in developed countries develop severe acute kidney injury (AKI) and receive an extracorporeal therapy, which aims to replace the kidney function. Such treatment logically goes by the term of Renal Replacement Therapy (RRT). Despite great advances in RRT, however, there was great controversy regarding the optimal intensity of such treatment. This controversy was based on the concept that standard RRT, at solute clearances typically between 20 and 25 ml/kg/hr may be inadequate. Although such clearances appeared to be sufficient to control volume status, the levels of biomarkers of uremic toxins such as urea and creatinine, potassium levels and acid-base status, a view developed that, if solute clearances were increased to 35-45 ml/min, better patient outcomes would follow. Data from pilot studies provided promising results and progressively began to encroach on clinical practice. However, it did so in the absence of a definitive trial. It was in this clinical and academic atmosphere that RENAL was conceived, designed, successfully submitted for funding, carefully prepared for, executed, and analysed. Its publication was a milestone in critical care nephrology and has had important repercussion on global practice. The preparation and actual trial results are presented in the first part of this thesis.

In addition to the above important impact of the RENAL trial, such a study (the largest study of AKI treatment in the world to date) collected a wealth of important information about patient treatment, biochemical and physiological information relevant to AKI. Thus, it provided a large data set that could be explored to better understand how one specific aspect of management may or may not show important associations with outcomes. In the second part of the thesis, three key studies assessing the association between RRT and fluid balance, acid-base and haemodynamic effects and phosphate control are explored. In addition, RENAL provided the most detailed information to date on nutritional therapy in severe AKI. Such information allowed the first comprehensive study of nutritional therapy during RRT and is presented in chapters 10 and 11. The RENAL trial collected important data on key medications that might affect renal function and renal recovery, like ACE inhibitors, and also provided detailed information on the timing of RRT initiation. Such information led to two specific investigations which are presented in chapters 12 and 13. Finally, the RENAL trial database collected important information on the technical characteristics of vascular access for the extracorporeal circuit and the transfusion of red cells. Such information has important implications for clinical practice and was investigated and reported in two studies which are presented in chapters 14 and 15.

In summary, this thesis provides an extensive view of multiple aspects of patient care in the setting of a pivotal randomized controlled trial of RRT in severe AKI. This comprehensive analysis is unique in this field and based on the largest dataset in the world. Its findings have had and continue to have major repercussions on global clinical practice in this field.

Declaration

This thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by any other person, except where due reference is made in the text of the thesis.

Rinaldo Bellomo

January 22nd, 2018

Publications during enrolment

R. Bellomo, A. Cass, L Cole et al. 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;26:407-416

R. Bellomo, A Cass, L Cole, et al. Renal replacement therapy for acute kidney injury in Australian and New Zealand intensive care units: a practice survey. Crit Care Resusc 2008; 10: 225-230

R. Bellomo, A. Cass, L Cole et al. Screening and study enrolment in the RENAL Replacement Therapy Trial. Blood Purif 2009;27:199-205

Finfer S, Cass A, Gallagher M, Lee J, Su S, **Bellomo R.** The RENAL (Randomized Evaluation of Normal vs. Augmented Level of Replacement Therapy) study: statistical analysis plan. Crit Care Resusc 2009; 11: 58-65

Bellomo R, Cass A, Cole L, et al. Intensity of continuous renal replacement therapy in critically ill patients. New Engl J Med 2009; 361: 1627-1638

Bellomo R, Cass A, Cole L et al. An observational study of fluid balance and patient outcomes in the randomized evaluation of normal vs augmented level of renal replacement therapy trial. Crit Care Med 2012; 40: 1753-1760

Bellomo R, Lipcsey M, Calzavacca P, et al. Early acid-base and blood pressure effects of continuous renal replacement therapy intensity in patients with metabolic acidosis. Intensive Care Med 2013; 39: 429-438

Bellomo R, Cass A, Cole L, et al. The relationship between hypophosphatemia and outcomes during low-intensity and high-intensity continuous renal replacement therapy. Crit Care Resusc 2014; 16: 34-41

Bellomo R, Cass A, Cole L, et al. Calorie intake and patient outcomes in severe acute kidney injury: findings from the randomized evaluation of normal vs. augmented level of replacement therapy (RENAL) study trial. Crit Care 2014; 18, R45

Jun M, **Bellomo R,** Cass A, et al. Timing of renal replacement therapy and patient outcomes in the randomized evaluation of normal versus augmented level of replacement therapy study. Crit Care Med 2014; 42(8):1756-65

Wang AY, **Bellomo R,** Ninomiya T, et al. Angiotensin converting enzyme inhibitor usage and acute kidney injury: a secondary analysis of RENAL study outcomes. Nephrology 2014; 19(10): 617-622

Bellomo R, Cass A, Cole L, et al. Daily protein intake and patient outcomes in severe acute kidney injury: findings of the randomized evaluation of normal versus augmented level of replacement therapy (RENAL) trial. Blood Purif 2014; 37: 325-334

Bellomo R, Martensson J, Lo S, et al. Femoral access and delivery of continuous renal replacement therapy dose. Blood Purif. 2015; 41: 11-17

Bellomo R, Martensson J, Kaukonen KM, et al. Epidemiology of RBC transfusions in patients with severe acute kidney injury: analysis from the randomized evaluation of normal versus augmented level study. Critical Care Med 2016; 44: 892-900

General declaration

In accordance with Monash University Doctor of Philosophy regulations, the following declarations are made.

I declare that to the best of my knowledge this thesis does not contain material accepted for the award of another degree at a university or equivalent institution and that, to the best of my knowledge and belief contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes 14 original publications published in peer-reviewed journals. The core theme of the thesis is to describe each and every known aspect so far of the largest trial of acute renal replacement therapy in the world. The ideas, development and writing up of all

papers in the thesis were the principal responsibility of myself, the student, working within the Monash University School of Public Health and Preventive Medicine under the supervision of Prof John McNeil.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research. Moreover, all studies were conceived, designed and overseen by myself. In multi-centre or multi-author studies I acted as the principal and senior investigator. I wrote or contributed in a major way to the initial draft of all manuscripts presented in the thesis and revised them in conjunction with co-investigators and members of relevant writing committees. In the case of chapters 2 to 15 my contribution involved the following:

Thesis Chapter	Publication Title	Status	Extent of candidate's contribution	Co-authors names Nature and % co-authors' contribution	Co-authors, Monash Students
2	Design and Challenges of the Randomized Evaluation of Normal versus Augmented Level Replacement Therapy (RENAL): High dose versus Standard-Dose Hemofiltration in Acute Renal Failure	Published	76% Concept and collecting data and writing of the first draft	All other members of the writing committee (Cass A, Cole L, Finfer S, Gallagher M, Goldsmith D, Myburgh J, Norton R, Scheinkestel C) all contributed 3% each to the drafting of the manuscript	No – for all co-authors
3	Renal replacement therapy for acute kidney injury in Australian and New Zealand intensive care units: a practice survey	Published	84% Concept and collecting data and writing of the first draft	All other members of the writing committee (Cass A, Cole L, Finfer S, Gallagher M, Goldsmith D, Myburgh J, Norton R, Scheinkestel C) all contributed 2% each to the drafting of the manuscript	No – for all co-authors
4	Screening and Study Enrolment in the Randomized Evaluation of Normal vs. Augmented Level (RENAL) Replacement Therapy Trial	Published	84% Concept and collecting data and writing of first draft	All other members of the writing committee (Cass A, Cole L, Finfer S, Gallagher M, Goldsmith D, Myburgh J,	No – for all co-authors

				Norton R, Scheinkestel C) all contributed 2% each to the drafting of the manuscript	
5	The RENAL (Randomised Evaluation of Normal vs. Augmented Level of Replacement Therapy) study: statistical analysis plan	Published	50% Concept, data analysis and redacting of initial draft	Cass A, Gallagher M, Lee J, Su S each contributed 5% to the preparation of the manuscript. Finfer S. contributed 30% to the preparation of the manuscript	No – for all co-authors
6	Intensity of Continuous Renal-Replacement Therapy in Critically Ill Patients	Published	56% Concept and data analysis, writing of the first draft	All other members of the writing committee (Cass A, Cole L, Finfer S, Gallagher M, Myburgh J, Norton R, Scheinkestel C, McArthur C, McGuiness S, Su S, Lo S) all contributed 4% each to the data analysis and drafting of the manuscript	No – for all co-authors
7	An observational study of fluid balance an patient outcomes in the randomized evaluation of normal vs. augmented level of replacement therapy trial	Published	67% Concept and data analysis writing of the first draft	All other members of the writing committee (Cass A, Cole L, Finfer S, Gallagher M, Lo S, McArthur C, McGuinness S, Myburgh J, Norton R, Scheinkestel C, Su S) all contributed 3% each to the drafting of the manuscript	No – for all co-authors
8	Early acid-base and blood pressure effects of continuous renal replacement therapy intensity in patients with metabolic acidosis	Published	66% Concept and data analysis writing of the first draft	Lipcsey M, Calzavacca P, Haase M, Haase-Fielitz A, Licari E, Tee A, Cole L, Cass A, Finfer S, Gallagher M, Lee	No – for all co-authors

				J, Lo S, McArthur C, McGuinness S, Myburgh J, Schienkestel C each contributed 2% to the review and final draft of the manuscript	
9	The relationship between hypophosphataemia and outcomes during low-intensity and high intensity continuous renal replacement therapy	Published	64% Concept and data analysis and writing first draft	Cass A, Cole L, Finfer S, Gallagher M, Inbyung K, Lee J, Lo S, McArthur C, McGuinness S, Myburgh J, Norton R, Scheinkestel C) all contributed 3% each to the drafting of the manuscript	No – for all co-authors
10	Calorie intake and patient outcomes in severe acute kidney injury: findings from the Randomized Evaluation of Normal vs. Augmented Level of Replacement Therapy (RENAL) study trial	Published	78% Concept and data analysis and writing first draft	Cass A, Cole L, Finfer S, Gallagher M, Lee J, Lo S, McArthur C, McGuinness S, Myburgh J, Norton R, Scheinkestel C) all contributed 2% each to the drafting of the manuscript	No – for all co-authors
11	Daily Protein Intake and Patient Outcomes in Severe Acute Kidney Injury: Findings of the Randomized Evaluation of Normal versus Augmented Level of Replacement Therapy (RENAL) Trial	Published	78% Concept and data analysis and writing first draft	Cass A, Cole L, Finfer S, Gallagher M, Lee J, Lo S, McArthur C, McGuinness S, Myburgh J, Norton R, Scheinkestel C) all contributed 2% each to the drafting of the manuscript	No – for all co-authors
12	Angiotensin-converting enzyme inhibitor usage and acute kidney injury: A secondary analysis of RENAL study outcomes	Published	55% Concept and redaction of first draft	Gallagher M, Ninomiya T, Lo S, Cass A, Jardine M, all contributed 3% each to the drafting of the manuscript. Wang A contributed 30% to the analysis and preparation of the manuscript	No – for all co-authors

13	Timing of Renal Replacement Therapy and Patient Outcomes in the Randomized Evaluation of Normal versus Augmented Level of Replacement Therapy Study	Published	55% Concept and data analysis and redaction of first draft	Cass A, Cole L, Gallagher M, Lo S, Lee J, all contributed 3% each to the drafting of the manuscript. Min J contributed 30% to the analysis of data and preparation of the manuscript	No – for all co-authors
14	Femoral Access and Delivery of Continuous Renal Replacement Therapy Dose	Published	58% Concept and data analysis and redaction of first draft	Cass A, Lo S, Kaukonen KM, Gallagher M, all contributed 3% each to the drafting of the manuscript. Martensson J contributed 30% to the data analysis and preparation of the manuscript	No – for all co-authors
15	Epidemiology of RBC Transfusions in Patients with Severe Acute Kidney Injury: Analysis from the Randomized Evaluation of Normal versus Augmented Level Study	Published	59% Concept a and redaction of first draft	Kaukonen KM, Lo S, Cass A, Cole L, Finfer S, Gallagher M, Myburgh J, all contributed 3% each to the drafting of the manuscript. Martensson contributed 20% to the data analysis and preparation of the manuscript	No – for all co-authors

I have not renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

January 22nd 2018

The undersigned hereby certifies that the above declaration correctly reflects the nature and extent of the student's and co-authors contribution to this work. In instances where I

am not the responsible author, I have consulted with the responsible author to agree on the respective contributions of the authors.

Main supervisor: John McNeil…….. Date……..

Acknowledgments

I wish to thank all my RENAL trial co-investigators and colleagues and collaborators in various participating ICUs. Without their help and dedication, this work would not have been possible. In particular, I wish to thank the team at the George Institute for International Health for providing important statistical and logistic support to make the trial practically possible. Finally, I wish to thank all the research coordinators, doctors and nurse who so diligently provided and collected the data and who so professionally delivered care to their patients, day in and day out.

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Chapter 1

The Randomized Evaluation of Normal vs. Augmented Level (RENAL) Replacement Therapy Trial

Introduction

When acute kidney injury (AKI) is severe, resolution can take several days or weeks. During this time, the kidneys may be unable to maintain homeostasis of fluid, potassium, metabolic acid, and waste products. If this pathophysiological state is prolonged, life-threatening complications frequently develop. In these patients, extra-corporeal techniques of blood purification become necessary to prevent such complications. These techniques broadly referred to as renal replacement therapy (RRT) include continuous haemofiltration and its technical variations, intermittent haemodialysis and its technical variations, and peritoneal dialysis and its technical variations. All of these techniques rely on the principle of removing unwanted solutes and water through a semipermeable membrane. Such membrane is either biological (peritoneum) or artificial (haemodialysis or haemofiltration membranes) and each technique offers several advantages, disadvantages and limitations.

PRINCIPLES

The principles of RRT have been extensively studied and described [1-3]. Nonetheless, in this introduction to the **RENAL trial** (for which I was privileged to be the lead and senior investigator**)** it is useful to summarise several key aspects, which are relevant to the trial itself.

Water removal

The removal of unwanted solvent (water) is therapeutically probably as important as the removal of unwanted solutes (acids, uraemic toxins, potassium and the like). During RRT, water is removed through a process called *ultrafiltration*. This process is essentially the same as that performed by the glomerulus. It requires a driving pressure to move water across a

semi-permeable membrane because such fluid would normally be kept within the circulation due to oncotic pressure. This pressure can be achieved by:

1. Generating a *transmembrane pressure* though the pumping of blood (as in haemofiltration or during intermittent haemodialysis) through the semipermeable membrane. This positive pressure is greater than the oncotic pressure that would retain water in the circulation and generates ultrafiltration.
2. Increasing osmolarity of the dialysate (as in peritoneal dialysis), which then draws water across the semipermeable membrane (the peritoneum) across an osmolar gradient

Solute removal

The removal of unwanted solutes (uraemic toxins, nitrogen waste products, organic acids) can in turn be achieved by

1. Creating an electrochemical gradient across the membrane using a flow past system with toxin free dialysate (*diffusion*) as in intermittent haemodialysis (IHD) and peritoneal dialysis (PD)
2. Creating a transmembrane pressure driven "solvent drag", where solutes move together with solvent (*convection*) across the membrane, are discarded together with the solvent and then replaced with toxin free replacement fluid as in haemofiltration (HF)

The rate of diffusion of a given solute depends on its molecular weight, the porosity of the membrane, the blood flow rate, the dialysate flow rate, the degree of protein binding, and its concentration gradient across the membrane. If synthetic high-flux membranes are used (cut-off at 10-20 kiloDaltons (kD) of MW in vivo) molecules with a MW below such cut-off

values can be removed. With these membranes, convection, however, is superior to diffusion in achieving the clearance of middle molecules (those with a MW>1000).

INDICATIONS FOR RENAL REPLACEMENT THERAPY

Prior to the **RENAL trial**, in the critically ill patient, there was significant controversy about the optimal timing of RRT. This controversy continues today. Fear of early RRT stems from historical experience with the adverse effects of conventional intermittent hemodialysis (IHD), especially haemodynamic instability, and from the risks and limitations of continuous or intermittent peritoneal dialysis (PD)[4-5]. However, continuous renal replacement therapy (CRRT)[6,7] or slow extended daily dialysis (SLEDD)[8] minimise these effects. Moreover, the criteria for the initiation of RRT in patients with chronic renal failure may not be appropriate in many critically ill patinets[9,10]. A set of modern criteria which can be considered sufficient for the initiation of RRT in the ICU was proposed prior to the RENAL trial is presented in Table 1. With either IHD or CRRT or SLEDD, there are limited data on what is “adequate” intensity of dialysis. However, the concept of dialytic adequacy should include maintenance of homeostasis at all levels[10] and better uraemic control may translate into better survival[11,12]. An appropriate target urea might be 15-25 mmol/L, with a protein intake around 1.5 g/kg/day. This can be easily achieved using CRRT at urea clearances of 20-25 ml/kg/hr depending on catabolic rate. If intermittent therapy is used, daily and extended treatment as described with SLEDD may be desirable in the ICU[13].

MODALITY OF RENAL REPLACEMENT THERAPY

Prior to the **RENAL trial,** there was a great deal of controversy as to which modality of RRT is "best" in the ICU, due to the lack of randomized controlled trials comparing different modalities (IHD or CRRT). In their absence, modalities of RRT were judged on the basis of the following criteria:

1. Haemodynamic side effects
2. Ability to control fluid status
3. Biocompatibility
4. Risk of infection
5. Uraemic control
6. Avoidance of cerebral oedema
7. Ability to allow full nutritional support
8. Ability to control acidosis
9. Absence of specific side effects
10. Cost

In relation to the above criteria, before the **RENAL trial**, CRRT and slow low-efficiency daily dialysis (SLEDD) offer many advantages over PD and conventional IHD (3-4 hours/day, 3-4 times/week)[13], and, therefore, CRRT or SLEDD were almost exclusively used in Australia and New Zealand ICUs[14], with IHD only being used prior to discharge or after discharge to the general wards. Irrespective of the choice of modality, some salient aspects of CRRT, IHD and PD, require discussion. This preference for CRRT in Australia and New Zealand (ANZ) and the infrequent use of IHD had a powerful impact on the design of the RENAL trial, as described in Chapter 2 of this thesis (*Design and challenges of the RENAL trial: High dose versus standard dose hemofiltration in acute renal failure. Blood Purif 2008; 26: 407-416*) and was confirmed

by an extensive survey of RRT practice in ANZ prior to the conduct of the trial as presented in Chapter 3 of this thesis (*Renal replacement therapy for acute kidney injury in Australia and New Zealand intensive care units: a practice survey. Crit Care Resusc 2008; 10: 225-230*). These two studies showed that, if a study was to be conducted in ANZ to test whether greater intensity of RRT increased survival in patients with severe AKI treated with RRT, such a trial would have to be based on CRRT as modality and should use the dominant technique of CRRT in ANZ at the time (continuous veno-venous hemodiafiltration – CVVHDF) (see Figure 1). Moreover, they demonstrated that the "standard" (normal) dose of CRRT in ANZ prior to RENAL trial approximated 25 ml/kg/hr of effluent generation during CVVHDF. This defined the "normal" value against which an increased dose had to be compared. The information obtained in these studies also defined the modality, technique and dose intensity for the intervention at 40 ml/kg/he of effluent generation with CVVHDF using the post-dilution technique in order to simulate the dose separation and intensity of phase II trials[15, 16] that had suggested that higher dose would increase survival in such patients and justified the conduct of a phase III trial like **RENAL.** In this regard, such phase II studies were the driving force to the conduct of the **RENAL trial.**

Once the design of the **RENAL trial** and the definition of standard and augmented levels of RRT intensity had been defined on the basis of ANZ evidence and practice and the trial had achieved funding by the National Health and Medical Research Council (NHMRC) recruitment was able to begin in 35 ICUs across both countries. The conduct of such a massive trial which aimed to randomize 1500 patients (the largest trial of acute kidney injury management in the world at the time and still the largest today), posed major logistic challenges. The overcoming of such logistic challenges as well a need to provide an understanding of patient screening process and recruitment efficiency motivated a detailed

investigation of the screening and study enrolment process during the trial. The findings of such investigation are presented in Chapter 4 (*Screening and study enrolment in the RENAL replacement therapy trial. Blood Purif 2009; 27: 199-205*). They provide a clear illustration of the effort required to conduct a trial of such magnitude in critically ill patients, with 4551 patients screened, 767 found ineligible and 2085 excluded because of the presence of specific exclusion criteria (especially end stage renal failure requiring dialysis prior to ICU admission; body weight <60 and >100 Kg and prior use of RRT during the index admission).

Another key aspect of a large phase III trial relates to the correct approach to the statistical analysis of the study findings. Accordingly, in order to enhance transparency, prevent informed adjustments to data analysis and adhere to best practice for such analysis, the statistical analysis plan (SAP) was published prior to the analysis of the study findings and is presented in Chapter 5 (*The RENAL study: statistical analysis plan. Crit Care Resusc 2009; 11: 58-66*). Such publication represented the final step in the preparatory academic work to the publication of the **RENAL trial** findings in the New England Journal of Medicine on October 22, 2009 as presented in Chapter 6 (*Intensity of continuous renal replacement therapy in critically ill patients. N Engl J Med 2009; 361: 1627-38*). The findings of the trial were clear and robust: increasing dose intensity did not affect mortality or any other secondary outcome. The **RENAL trial** together with a germane trial of 1124 patients conducted in the USA at approximately the same time[17], which also found no beneficial effect from increasing dialysis intensity led to definitive changes to worldwide practice, guidelines and recommendations, which have defined and continue to define modern RRT practice globally. In ANZ, where the pre-RENAL trial survey confirmed the use of high intensity (40 mml/kg/hr or higher) in approximately 50% of centres, the **RENAL trial** has changed practice to the

binational application of 25 ml/kg/hr. Given that an estimated 1500 patients receive acute RRT in ICU in Australia every year, this observation implies that 750 of such patients every year who would have continued to receive higher dose (40 ml/kg/hr) now receive standard dose (25 ml/kg/hr). The RENAL trial found that the average weight of randomized patients was approximately 80 kg, implying that higher dose intensity would deliver 3.2L of replacement fluid per hour instead of 2 L per hour with standard dose. Over a an average operative time of CRRT of 20 hours/day, this difference translates into an extra 1.2 L x 20 hrs each day (24 extra litres/day of replacement fluid). Moreover, given that the average duration of CRTT for such patients was approximately 6 days, it implies a difference of 24 x 6 L (144 litres) per patients being required to replace the additional effluent being generate with higher dose CRRT. In ANZ, this would translate into 144 liters x 750 patients/year or 108,000 extra litres being used at approximately four dollars per litre: an estimated saving of 432,000 dollars/year, which over the last 6 years, has saved 2,592,000 dollars to the health care system and more than paid off the cost of funding the trial.

However, beyond such health economics considerations, like all large trials, the **RENAL trial** has been a major source of crucial additional information that has influenced practice, thinking, hypothesis generation, and subsequent trial design worldwide. Such additional information or trial data analysis was pursued systematically after the publication of the trial to address important questions that had arisen from the letters, public comments, editorials, presentations, debates and opinion pieces that followed its publication.

The first such investigation sought to address the issue a fluid management during RRT and is presented in Chapter 7 (*An observational study of fluid balance and patient outcomes in the randomized evaluation of normal vs. augmented level of replacement therapy trial. Crit Care Med 2012; 40: 1753-1760*). This study was the first to demonstrate a strong

independent association between a negative daily fluid balance and decreased risk of death at 90 days (Odds ratio: 0.318, 95% CI 0.24-0.43, p<0.0001). Such observations spawned several subsequent studies, all of which confirmed such findings. In the aggregate, these findings have contributed to the worldwide movement toward to tighter volume control in critically ill patients with acute kidney injury (AKI).

A second additional analysis of RENAL trial data focused on the potential for higher intensity CRRT to influence the early acid-base status of patients with metabolic acidosis, as presented in Chapter 8 of this thesis (*Early acid-base and blood pressure effects of continuous renal replacement therapy intensity in patients with metabolic acidosis. Intensive Care Med 2013; 39: 429-436*). This additional analysis demonstrated that in patients with metabolic acidosis (mean base deficit of 8 mEq/L), the speed of correction of acid-base status was not different between standard dose and higher dose CRRT. However, it also demonstrated that higher dose CRRT provides a hemodynamic advantage in such patients with a greater decrease in norepinephrine dose and a greater increase in mean arterial pressure. These findings are of clinical relevance to those patients who are hypotensive and vasopressor dependent in the setting of severe metabolic acidosis, a unique a high risk group of patients with AKI.

A third focus of investigation relates to a specific metabolic effect of CRRT (hypophosphatemia) and is presented in Chapter 9 (*The relationship between hypophosphatemia and outcomes during low-intensity and high-intensity continuous renal replacement. Crit Care Resusc 2014; 16: 34-41*). Phosphate is typically elevated in patients with AKI because its normal renal clearance has failed. However, it is removed by CRRT with

clearances similar to those of creatinine. Therefore, it is logical to expect that higher intensity CRRT would increase the risk of hypophosphatemia. In addition, it is possible that such hypophosphatemia may show an independent relationship with increased risk of death. This study confirmed that CRRT exposes AKI patients to the risk of hypophosphatemia with a peak effect on day 2 and day 3, with a much greater incidence of this derangement in patients treated with higher intensity CRRT. In addition, this study was able to identify risk factors for hypophosphatemia, which could be sued to identify higher risk patients who should receive early prophylactic replacement. However, it also found that patients who developed hypophosphatemia did not appear to have a significant increase in the risk of death. A potential explanation for this surprising finding is that another powerful determinant of phosphate levels in critically ill patients is the delivery of nutrition. Thus, patients able to receive adequate nutritional therapy are also a higher risk of hypophosphatemia (selection bias toward a group with better outcome because of their ability to tolerate feeding). These considerations led to the need to explore the nutritional aspects of management applied during the **RENAL Trial.**

The first component of nutrition investigated in an additional analysis of the data from the **RENAL trial** focused on calorie intake and is presented in Chapter 10 (*Calorie intake and patient outcomes in severe acute kidney injury: findings of the RENAL study trial. Crit Care 2014; 18: R45*). This study found that that caloric intake during CRRT was low at less than 50% of prescribed dose. However, within the limitations of such seemingly inadequate level of nutritional therapy greater caloric intake showed a trend toward better outcome. Such finding have contributed to the debate surrounding the optimal caloric intake in critically ill patients, which has generate several key nutritional trials since.

The second component of this nutritional assessment of the RENAL trial relates to protein intake and its association with outcome and is presented in Chapter 11 (*Daily protein intake and patient outcomes in severe acute kidney injury: findings of the RENAL trial. Blood Purif 2014; 7: 325-334*). This study found that, just like in the case of calorie intake, daily protein intake during the trial was low at less than 0.5 g/kg/day, well below recommended dose. However, it also found, that within the confines of a generally low intake, daily protein intake was no independently associated with increased risk of death.

An important aspect of patient management in the setting of AKI requiring RRT relates to the potential effect of drugs like angiotensin converting enzyme inhibitors (ACEI) that have been shown to both decrease GFR in some patients and protect against long-term loss of renal function in others. In a study presented in Chapter 12 (*Angiotensin-converting enzyme inhibitor usage and acute kidney injury: a secondary analysis of RENAL study outcomes. Nephrology 2014; 19: 617-622*) 142 patients were identified who received ACEI therapy. Such patients were older but also less likely to have sepsis and also appeared to have a more favourable outcome. Importantly, however, using time-dependent analysis, ACEI did not have any effect on mortality.

An issue of great importance in the management of patients with severe AKI relates to the timing of intervention with two schools of thought. One advocates early intervention to prevent or very rapidly treat any physiologic derangements associated with AKI. The other emphasizes the risks of extracorporeal circulation and advocates an approach of judicious delay with intervention only when more conventional criteria for dialysis are present. The data obtained from the **RENAL trial** offered a great opportunity to assess the potential

differential impact on patient outcomes of the timing of initiation of RRT as described in Chapter 13 (*Timing of renal replacement therapy and patient outcomes in the randomized evaluation of normal versus augmented levels of replacement therapy study. Crit Care Med 2014; 42: 1756-1765*). In this sub-study of the **RENAL trial**, there was clear evidence that ANZ ICU clinicians practice early initiation of RRT with the median time from ICU admission to initiation of RTT at only 16.6 hours. However, there was also no evidence that such early initiation was an independent predictor of outcome suggesting the presence of equipoise and the need for a dedicated large trial to address this issue. In fact, two medium sized studies have since sought to address this issue and have proved inconclusive [18,19] and a pivotal trial of >2,000 people is now under way.[20]

The **RENAL trial** also enabled the exploration of practical issues of technique including the choice of site for the insertion of the necessary double-lumen catheter used for CVVHDF and the length and characteristics of such catheter which would positively affect circuit life. AS described in Chapter 14 (*Femoral access and delivery of continuous renal replacement therapy dose. Blood Purif 2016; 41: 11-17*), femoral venin was chosen as the first site for RRT double-lumen catheter insertion in two thirds of patients and its preferentially inserted in such site in more acutely ill and thinner patients. Such access was associated with slight but clinically unimportant decrease in circuit life. In contrast larger double lumen catheters (Size 13.5 French) had a more important impact with better circuit life with their insertion and use.

Finally, an important issue in patients with severe AKI is whether there is a relationship between the transfusion of red cells and outcome. This area which has been widely explored

in critically ill patients in general, had never been studied in this unique population of patients. In critically ill patients, the transfusion of red cells has been independently associated with greater risk of death. However, patients with severe AKI have unique features, including the anemia of renal disease and a particularly low level of erythropoietin levels, which suggest that might more significantly depend on the administration of red cells. As reported in Chapter 15 (*Epidemiology of RBC transfusions in patients with severe acute kidney injury: analysis from the RENAL study. Crit Care Med 2016; 44: 892-900*), two thirds of patients received red cell transfusions. However, contrary to expectations, mortality was the same for transfused vs. non-transfused patients and even after multiple adjusted analyses, no convincing evidence of association with harm was seen with red cell transfusion, suggesting that, in these patients, there may be a unique and different relationship between red cell administration and outcome.

As shown above, multiple peer-reviewed publications in key specialty journals have already been produced with significant contributions to our knowledge of this area. However, more analyses are planned and some are already under way. After 8 years of publications, the **RENAL trial** continues to provide important insights into practice and outcomes in some of the sickest patients in the intensive care unit. As initiator, lead and senior investigator in these studies I feel I have been uniquely privileged to be able to explore so many aspects of such a complex disease and to contribute so many studies to a rapidly evolving area, which have helped shape the practice and research agenda for close to a decade.

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Table 1: Modern criteria for the initiation of RRT in the ICU*

1. Oliguria (urine output < 200 ml/12 hours)
2. Anuria (urine output: 0 to 50 ml/12 hours)
3. [Urea] > 35 mmol/L
4. [Creatinine] > 400μmol/L
5. $[K^+]$ > 6.5 mmol/L or rapidly rising^
6. Pulmonary oedema unresponsive to diuretics
7. Uncompensated metabolic acidosis (pH<7.1)
8. $[Na^+]$ < 110 and >160 mmol/L
9. Temperature > 40^oC
10. Uraemic complications (encephalopathy/myopathy/neuropathy/pericarditis)
11. Overdose with a dialyzable toxin (eg. Lithium)

**If one criterion is present, RRT should be considered. If two criteria are simultaneously present, RRT is strongly recommended.*

^Please be aware of differences between plasma vs. serum measurement in your laboratory

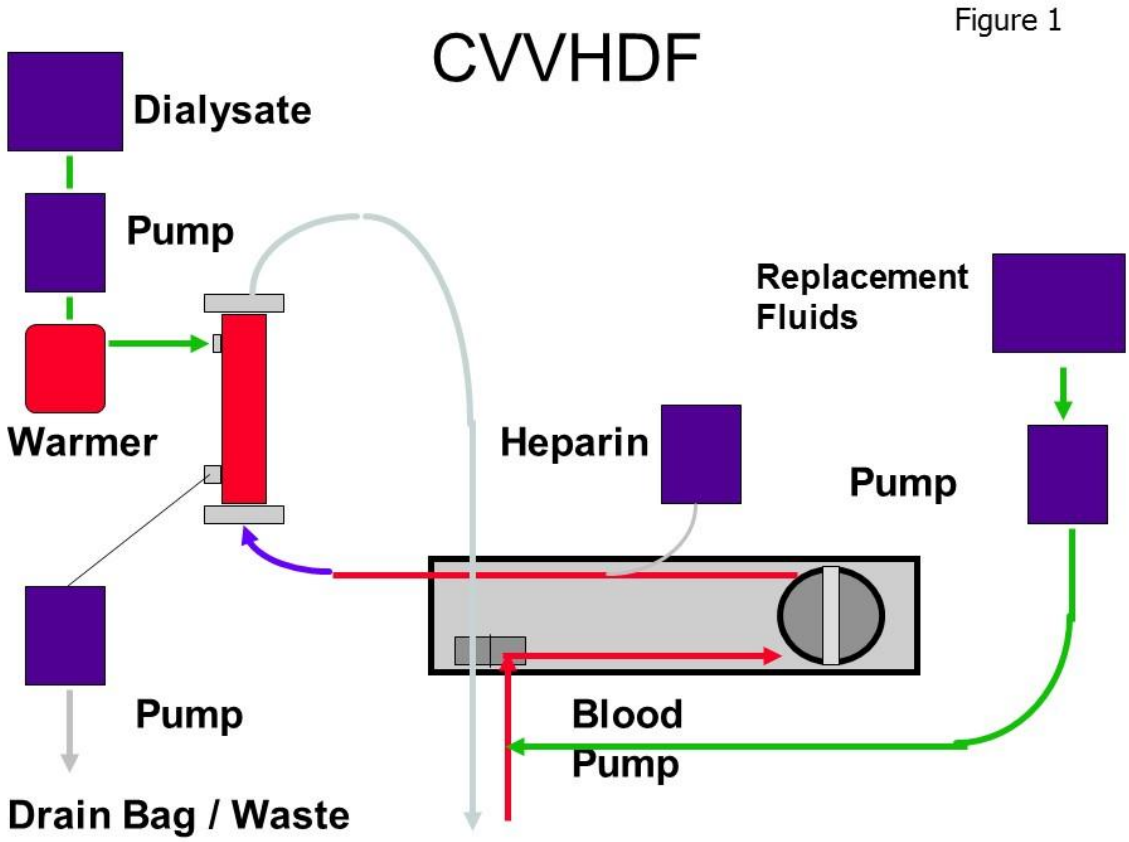

Figure 1: Diagrams illustrating a continuous veno-venous haemodiafiltration circuit (CVVHDF)

Chapter 2

Design and Challenges of the Randomized Evaluation of Normal versus Augmented Level Replacement Therapy (RENAL): High dose versus Standard-Dose Hemofiltration in Acute Renal Failure

Review

Blood Purification

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Design and Challenges of the Randomized Evaluation of Normal versus Augmented Level Replacement Therapy (RENAL) Trial: High-Dose versus Standard-Dose Hemofiltration in Acute Renal Failure

The RENAL Study Investigators[1]

Key Words
Intensive care · Acute renal failure · Dialysis · Continuous hemodiafiltration · Renal replacement therapy, continuous · Kidney

Abstract
Background/Aims: The optimal dose of renal replacement therapy (RRT) in acute renal failure (ARF) is uncertain. ***Methods:*** The Randomized Evaluation of Normal versus Augmented Level Replacement Therapy Trial tests the hypothesis that higher dose continuous veno-venous hemodiafiltration (CVVHDF) at an effluent rate of 40 ml/kg/h will increase survival compared to CVVHDF at 25 ml/kg/h of effluent dose. ***Results:*** This trial is currently randomizing critically ill patients in 35 intensive care units in Australia and New Zealand with a planned sample size of 1,500 patients. This trial will be the largest trial ever conducted on acute blood purification in critically ill patients. ***Conclusion:*** A trial of this magnitude and with demanding technical requirements poses design difficulties and challenges in the logistics, conduct, data collection, data analysis and monitoring. Our report will assist in the development of future trials of blood purification in intensive care. This study was registered with ClinicalTrials.gov (NCT00221013).

Introduction

In 2000, the *Lancet* published a single-center randomized trial suggesting that augmenting the dose of continuous renal replacement therapy (CRRT) in critically ill patients with acute renal failure (ARF) achieved a significant reduction in short-term mortality [1]. Ronco and colleagues randomized 425 ICU patients with severe ARF to receive one of three treatments using the CRRT technique of continuous veno-venous hemofiltration (CVVH): (1) CVVH at 20 ml/kg/h of effluent (low dose); (2) CVVH at 35 ml/kg/l of effluent (higher dose), and (3) CVVH at 45 ml/kg/h of effluent (highest dose). Survival in the low-dose treatment patients was significantly lower than in the higher-dose treatment patients and/or the highest-dose patients.

At the time of designing the Randomized Evaluation of Normal versus Augmented Level Replacement Therapy Trial (the RENAL trial, 2005), additional support for the findings that increasing the dose of renal replacement therapy (RRT) might improve survival had emerged from a number of animal and human studies. Such support included indirect evidence from patients with chronic renal

[1] The names of the RENAL Study Investigators are listed in the Appendix.

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failure that, within a defined range, a higher dose of dialysis was associated with increased survival [2]; a retrospective analysis of the outcome of a large cohort of intensive care unit (ICU) patients with severe ARF at the Cleveland Clinic [3] showed that patients treated with a greater dose of dialysis had increased survival; a randomized controlled trial [4] comparing daily to second-daily dialysis demonstrated a survival advantage for the higher-intensity daily dialysis; a randomized controlled trial comparing continuous hemofiltration to peritoneal dialysis in ICU patients showed a survival advantage for the increased-dose regimen delivered with hemofiltration [5]; animal studies of high-volume hemofiltration in experimental sepsis and septic shock [6, 7] demonstrated improvement in hemodynamics with high-dose treatment, and phase I human studies of higher-intensity treatment (60–80 ml/kg/h of effluent) showed similar physiological effects and possible clinical outcome benefits [8, 9].

Whilst these studies collectively made a strong case for delivering higher-dose CRRT, some evidence was available in 2005 that was not supportive. Two recent studies in the chronic renal failure setting cast doubt on the suggestion that survival could be improved by increasing the dose of dialysis. A Mexican group of investigators conducted a multicenter, prospective, randomized controlled trial of the effects of increased peritoneal clearances on mortality in peritoneal dialysis patients [10]. This study demonstrated no clear survival advantage with increased dose. Similarly, a large multicenter randomized controlled trial of hemodialysis performed in the USA [11] found that increasing hemodialysis dose in patients receiving chronic hemodialysis conferred no significant improvement in mortality.

Globally, the higher dose ranges for CRRT dose proposed by Ronco et al. [1] were not embraced [12] in the acute setting for a variety of reasons. First, the study was conducted unblinded at a single center over 5 years. Second, the study population had a low incidence of sepsis, in contrast with international populations where sepsis is the predominant cause of ARF. Third, there were concerns about the additional cost of intensifying therapy (USD 150–200/day). Fourth, there was concern that increasing dialysis dose may lead to large and difficult to assess nutrient losses. Fifth, the study provided limited information on the ancillary care of patients, and finally, the study used an unusual primary outcome measure (survival 15 days after discontinuation of treatment) and provided no evidence of secondary outcome benefits.

Thus, in 2005, there appeared to be a possibility that increasing the dose of acute RRT might significantly increase survival but, as yet, this treatment has not been widely adopted. In response to this uncertainty, we designed, obtained funding for and began to conduct a phase III multicenter, randomized controlled trial comparing CRRT at a dose of 40 ml/kg/h of effluent with CRRT at a dose of 25 ml/kg/h of effluent. The aim of this trial was to provide high-quality evidence about the comparative effects of different levels of CRRT dose in patients with ARF treated in the ICU. This evidence will have direct relevance to decisions about the care of critically ill patients worldwide. If this study shows a benefit similar to the Ronco study, given the current incidence of severe ARF, it may save an estimated 15,000 lives/year worldwide.

Common to other large-scale clinical trials in ICUs and because of the additional issues related to blood purification technology, however, RENAL posed some unique and major challenges. Understanding their nature and how they were addressed may assist with the conduct of similar complex studies in the future. Accordingly, here we describe several important aspects of this study and how we met some of its challenges.

Ensuring an Ethical and Representative Control Treatment

There has been growing concern that investigators must ensure that the control group of any ICU trial will receive a level of care which represents current practice [13]. This is particularly important in the ICU because decisions about trial participation have to be made over a short period of time, the patient is typically unable to consent and the patient's representative has to act on his/her behalf with limited time to consider the available options. Accordingly, as a prelude to this study, the Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group (CTG) conducted a survey of CRRT practice in Australian and New Zealand (ANZ) ICUs. This survey included all intended trial hospitals and showed the following findings:

1 More than 98% of ICUs in ANZ treated ARF exclusively with CRRT, not intermittent hemodialysis.
2 Eighty-six percent of units prescribed a 'fixed' standard dose of 2 liters/h of effluent or less which was not adjusted for body weight.
3 Continuous veno-venous hemodiafiltration (CVVHDF) was the most common CRRT technique.
4 The median estimated body weight among ANZ patients receiving CRRT was 80 kg and not 70 kg as usually assumed.

5 Accordingly, the standard dose of dialysis (2 liters/h of effluent) was typically 25 ml/kg/h.
6 CRRT was associated with significant circuit down times [14] that effectively reduced the mean 'dose' of CRRT from the typically 'prescribed' dose of 25 ml/kg/h.

Accordingly, the average total daily treatment dose received by most people in ANZ at the time of the survey before the trial was approximately 25 ml/kg/h, a value slightly above the median worldwide [12]. For the RENAL study, this meant that randomizing patients to a control group at a 20 ml/kg/h dose of CRRT (as done in Ronco's study) would have been unethical. On the other hand, a dose of 25 ml/kg/h of CRRT reasonably represented current practice in ANZ and was ethically justifiable.

Selecting Study Treatments

In addition to the survey results, to achieve feasibility, dose separation, clinical relevance and reproducibility, the choice of CRRT for the two arms of the study had to be based on the following principles:

1 The intervention dose should be the average of the two higher-dose treatments found to achieve improved outcomes in the *Lancet* study.
2 The dose difference between the treatment and control arms should be 15 ml/kg/h, the same as in the *Lancet* study.
3 The control arm should deliver a dose which reflected current practice.
4 The technique of CRRT should be the same for both the normal and augmented dose arms of the study.
5 The technique of CRRT should be deliverable using the machines available in ANZ ICUs at the time of inception.

As a result, it was agreed that patients in the control arm should receive CVVHDF at 25 ml/kg/h of effluent flow rate and that the intervention arm should receive CVVHDF with the generation of 40 ml/kg/h of effluent. For both treatments, it was agreed that dialysate flow and post-filter fluid replacement should be delivered in equal amounts (50% dialysate and 50% replacement fluid) in order to comply with the above requirements. The ratio of 1:1 for dialysate and replacement fluid flow represented current practice in ANZ. However, the relatively common practice of delivering replacement fluid in the prefilter position had to be changed to avoid the solute dilution effect of such an approach. This effect would lead to greater solute dilution (and decreased urea and creatinine clearance) with 40 ml/kg/h of CRRT dose compared to 25 ml/kg/h and would significantly diminish the dose separation between the two treatments. Accordingly, it was agreed that post-filter replacement fluid administration was necessary.

Other Technical Issues

CVVHDF is a complex blood purification technique and correct application of this technique required that several technical aspects be dealt with in a way that ensured feasibility, clinical relevance and reproducibility.

Anticoagulation

CVVHDF circuits typically require anticoagulation to prevent filter clotting [12]. The method of anticoagulation varies from patient to patient and from institution to institution. To ensure patient safety, feasibility and clinical relevance, it was decided that choice of anticoagulation should be left to the treating clinician and recorded.

Replacement and Dialysate Fluid Choice

Replacement and dialysate fluids are produced commercially and come with different buffers (lactate, citrate and bicarbonate). The nature and concentration of the buffer can have profound effects on acid-base balance and, most notably, high doses of lactate-based fluids can induce hyperlactatemia [15]. Using lactate-based fluids in the study would have led to a differential effect on blood lactate between the two study groups and may have generated a major confounder. Accordingly, despite the additional cost, the investigators agreed that all patients should receive CVVHDF using bicarbonate-based fluids with an identical concentration of bicarbonate.

Weight

The RENAL investigators decided that patient weight would be measured directly wherever possible. If this was not possible, it was agreed that it should be estimated using a variety of sources of information (medical records, family, height-based assessment) as was done for the *Lancet* study.

Membranes

Membranes for CRRT have variable composition (modified cellulose, polyacrylonitrile, polysulfone, polyamide). These different compositions can produce quite different blood-membrane interactions and biological

Table 1. Criteria to justify randomization in the presence of a clinical decision that RRT was needed

Oliguria (urinary output <100 ml/6 h)
Hyperkalemia (>6.5 mmol/l) secondary to ARF
Acidemia (pH <7.2) associated with ARF
Azotemia (urea >25 mmol/l or creatinine >300 μmol/l)
Refractory pulmonary edema associated with ARF
Uremic encephalopathy or pericarditis or neuropathy/myopathy

consequences. Accordingly, it was necessary to ensure that all patients were treated with the same membrane. We conducted a survey and found that the AN69 (polyacrylonitrile) membrane was used by >80% of study centers and that 70% of centers used the Prisma CRRT machine. These factors made it necessary to mandate the use of AN69 membrane in both groups.

Machines

As different units used different machines and as there was no reason to believe that machine choice would affect clearance in any specific way, different ICUs were allowed to use whatever CRRT machines were available to them, as long as they could deliver the trial therapy.

Blood Flow

It was agreed that target blood flow should be set at >150 ml/min. Blood flows of at least 150 ml/min were needed to ensure adequate small solute equilibration in the high-dose group. In addition, because replacement fluid was delivered post-filter, it was necessary to ensure sufficient blood flows to avoid marked hemoconcentration in the high-dose group. Such hemoconcentration would be expected to decrease filter life and possibly increase 'down time' for the high-dose circuits. This phenomenon could, in turn, decrease clearances in a way that reduced the differences in study treatments. It was felt that this approach to blood flow would minimize this possible bias.

Dialysis Catheters

Differences in patient size and associated risk of central venous catheter insertion require clinical judgment; thus decisions regarding the choice of catheter size (11.5 Fr or above) and access site were left to the discretion of the treating clinicians.

Ancillary Care

As this was a study of acute RRT, there was no intention of regulating other practices not related to RRT per se. However, an investigator brochure was issued to highlight important aspects of general patient care related to the two different doses. These aspects included antibiotic dose adjustments and nutritional adjustments that might derive from amino acid losses, phosphate losses, vitamin losses and trace element losses.

Ensuring a Representative Study Population

The RENAL study inclusion and exclusion criteria had to fulfill the following requirements: simplicity, clinical relevance and applicability to the majority of patients currently receiving CRRT in ANZ. As such, patients were excluded from the study if they were treated with CRRT for reasons other than ARF (overdose of drugs, temperature control, adjuvant treatment of sepsis); were less than 18 years old, were about to die, were already receiving dialysis for end-stage renal failure, or were unable to receive the protocol as planned or had been previously treated with acute dialysis. These issues were summarized in three principles of inclusion:

1 The treating clinician should believe that the patient requires CRRT for ARF.
2 The patient should fulfill at least one of several criteria for initiating acute CRRT (table 1).
3 The clinician should be uncertain about the balance of benefits and risks likely to be conferred by treatment with higher intensity or lower intensity CRRT. This 'uncertainty principle' has been used to guide patient inclusion in many other large trials in seriously ill patients [16].

We excluded the following patients: (1) age <18 years; (2) imminent (<24 h) death; (3) strong likelihood that the study protocol could not be delivered; (4) previous CRRT or dialysis during this hospital admission; (5) end-stage renal failure (patient receives chronic dialysis), and (6) the patient's body weight is <60 or >100 kg (technology limit).

The weight upper limit was later altered to 120 kg (by formal trial amendment) as technology to deliver a higher dose in such patients became widely available in ANZ. The choice of a lower weight limit was dictated by the need to ensure that no patient would receive <1.5 liters/h of effluent, the lowest level delivered in ANZ ICUs prior to the trial.

Ensuring Appropriate Sample Size and Power

The treatment effect observed in the *Lancet* study was a reduction in mortality from 59 to 42% (29% relative re-

duction and 17% absolute reduction in mortality). We assumed a conservative 90-day mortality rate of 60% in our control group [17]. We also assumed a conservative estimate for the relative reduction in mortality in patients which was half that reported in the *Lancet* study (i.e. 14.5%) and a parallel absolute reduction in mortality of 8.5%. Based on these figures, we calculated that a study of 1,500 patients would have a 90% power of detecting an 8.5% absolute reduction from a 90-day mortality of 60% in the control group to 51.5% in the intervention group ($\alpha < 0.05$). Such a difference is clinically significant (number needed to treat = 12) and would likely lead to a widespread change in the practice of CRRT around the world. As the additional cost of the extra fluid needed is easily calculated and the average duration of therapy is approximately 5 days, this treatment would be highly cost effective at USD 12,000/life saved.

Blinding

To ensure patient safety, fluid removal and fluid replacement during CRRT must be closely monitored and the results known to the clinical staff treating the patients. As patient safety was considered paramount, it was not possible to design a study that would blind clinical staff to treatment allocation. It was considered that bias would be minimized by ensuring adequate concealment of treatment allocation prior to central randomization and by the use of robust, objective outcome measures such as all-cause, 90-day mortality. As the primary outcome was death, which is 100% verifiable, it was also not considered to be subject to ascertainment bias.

Table 2. Major items for data collection during the RENAL trial

At baseline and before randomization
Patient identifiers
Key clinical characteristics
Inclusion and exclusion criteria
APACHE III and SAPS II or III? scores (intensive care, severity of illness scores)
Previous history of renal dysfunction
Pretreatment urea, creatinine, electrolytes and acid-base variables
Timing of start of CRRT
Urine volume
Body weight
During follow-up in the intensive care unit
Daily urea, creatinine
Daily morning electrolytes and acid-base variables
Daily fluid balance
Daily nutritional intake
Type of machine used
Type and site of vascular access
Anticoagulation mode and dose
Filter life
Time spent off filtration daily
Complications of CRRT
Need for inotropic/vasopressor agents and/or positive pressure ventilation
Deaths and nonfatal serious adverse events
After live discharge from the intensive care unit
Vital status at ICU and hospital discharge
Vital status 28 and 90 days after randomization (for all patients who die during follow-up, information about the cause of death will be sought from collaborating centers)
Data on the use and duration of intermittent dialysis

Randomization and Allocation of Treatment

Subjects had a 50% chance of being allocated to either the normal or augmented dose treatment group. The George Institute for International Health managed the web-based randomization via a secure password-protected, encrypted, web-based interface. The sequence was concealed until treatment was assigned. This system was available 24 h/day and 7 days/week.

Duration of Treatment

An important decision was related to the cessation of study treatment. The guiding principles were to ensure that standard practice should be altered as little as possible and that the study treatment should be given for as long as possible within such constraints. Accordingly, study treatment should continue until one of the following events applied: (1) death; (2) discharge from ICU; (3) the clinician considered that CRRT could be ceased *and* the patient had a spontaneous urinary output of at least >400 ml over the preceding 24 h, and (4) in the absence of criteria 1, 2, or 3, until at least 1 week had passed from randomization *and* the patient no longer required endotracheal intubation *and/or* vasopressor support.

Patients withdrawn from the randomized treatment for any reason were to be followed up according to the study follow-up schedule and analyzed according to the intention-to-treat principle. Once the study treatment ceased, further renal replacement was prescribed at the discretion of the clinical staff managing the patient. If the patients return to CRRT within 90 days after randomization, if clinically appropriate, they will return to treat-

Table 3. Secondary outcomes (all to be determined at 90 days and in relation to the index ICU admission)

Death in the intensive care unit
Death within 28 days of randomization
Death prior to hospital discharge
ICU-free days
Hospital-free days
Mechanical ventilation-free days
Vasopressor drug-free days
CRRT-free days
RRT-free days
Dialysis-independent survival at 90 days

ment with the previously assigned dose. RRT required after ICU discharge would be prescribed at the discretion of the clinical staff managing the patient and the type of dialysis, its frequency, duration and timing of cessation would be recorded.

Study Outcomes

The primary study outcome was set as all-cause mortality 90 days after randomization. Every randomized patient was to be followed up until either death or 90 days after randomization as recommended by the UK Medical Research Council International Working Party for Clinical Trials in Patients with Sepsis and Septic Shock [1]. Recent data indicate that mortality for patients with ARF reaches a plateau at between 60 and 90 days [17]. Secondary outcomes are presented in table 3.

Adverse Events

The ICU environment poses major challenges to the identification of relevant adverse events as major derangements of physiology and clinical condition are daily occurrences. As the treatments under investigation are well-established as are their side effects, investigators were directed to report those adverse events they felt were potentially related to trial treatment.

Data Collection and Follow-Up

Streamlined data collection instruments and procedures were developed to minimize the work for collaborating centers. Data collection was restricted primarily to those variables necessary to define patient characteristics at baseline, the incidence and severity of biochemical abnormalities related to renal function, the timing of treatment initiation, the daily monitoring of biochemical and acid-base control, nutritional intake, fluid balance, post-CRRT trial RRT (hemo- or peritoneal dialysis) and documentation of deaths and other serious adverse events during follow-up (table 2).

Data Quality Assurance

Investigators agreed that an independent, trained and qualified representative of the George Institute for International Health would monitor the conduct of the study by visiting the sites. During the visits, information would be verified against source documents.

Informed Consent

Obtaining written and informed consent from patients the ICU is complicated because Intensive Care patients are often unconscious, sedated, intubated or too ill to understand information relating to clinical trial participation. The Declaration of Helsinki recognizes that some clinical research will involve patients who are physically incapable of giving informed consent (Principle 26, World Medical Association Declaration of Helsinki, 2000). For critically ill patients who were not able to provide consent, an explanatory statement was to be provided to their legal surrogate at the earliest opportunity, with additional consent from the necessary authorities (civil and administrative tribunals) as required by state or territory legislation or obtained from a legal surrogate when allowed by such legislation in ANZ. According to legislation, it was agreed that the participant information sheet would be provided to the patient when and if they regained legal capacity and were able to make an informed decision concerning continued participation in the study. Unless specifically prohibited by the patient or their legal surrogate, follow-up data was to be collected to day 90.

Analysis of Results

Analyses will be performed by independent statisticians on an intention-to-treat basis. Accordingly, at interim and final analysis, the baseline variables will be

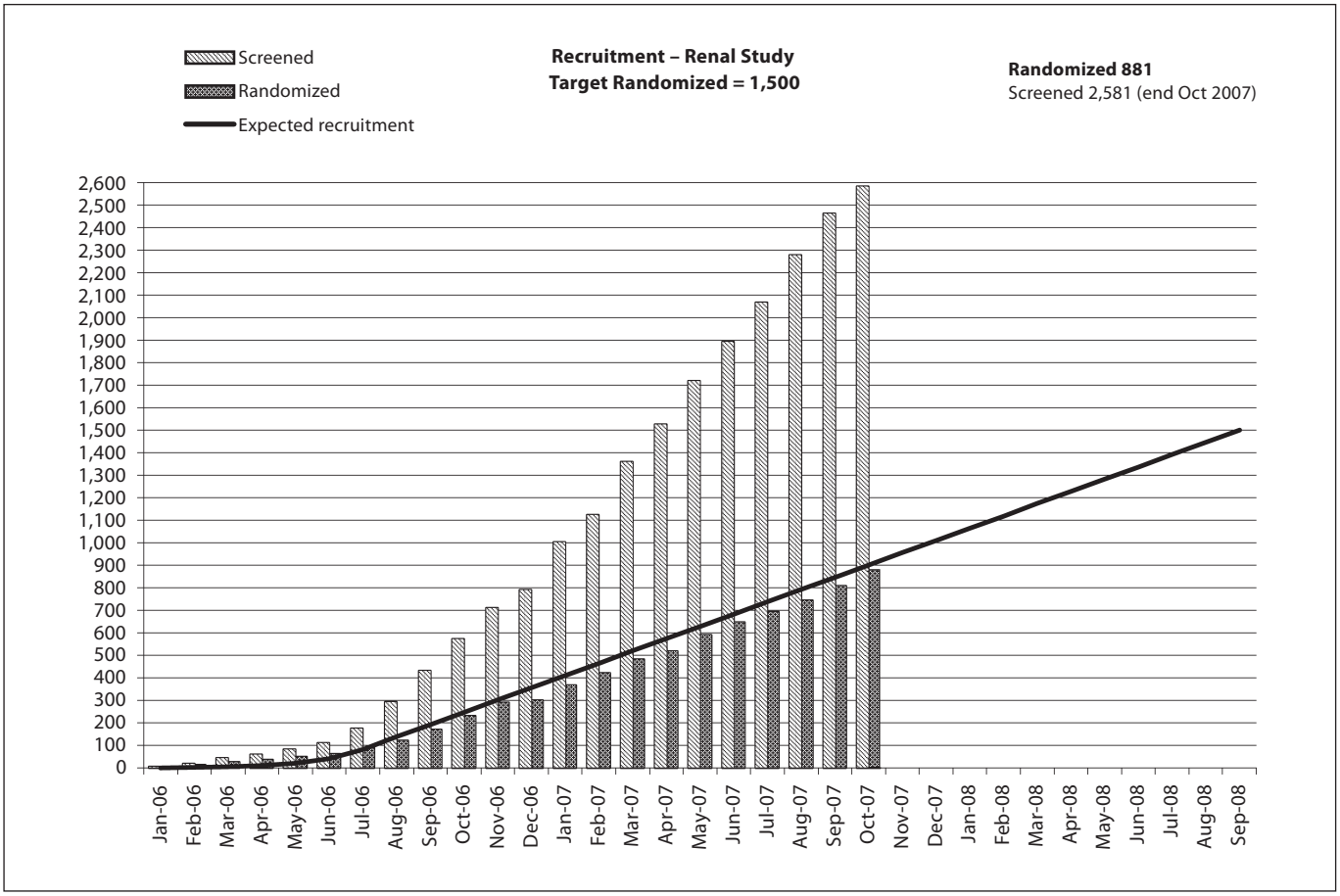

Fig. 1. RENAL trial recruitment.

summarized using descriptive statistics (means, standard deviations for continuous variables, frequencies and percentages for categorical endpoints). Mortality outcomes will be compared across treatment arms using a χ^2 test or a Fisher exact test as appropriate. Survival times at days 28 or 90 will be assessed by means of the log-rank test and presented as Kaplan-Meier survival curves. A measure of effect with its 95% confidence interval will also be reported; relative risk/hazard ratio or difference in means/proportions will be reported as appropriate.

Data and Safety Monitoring Committee

An independent Data and Safety Monitoring Committee, comprising experts in clinical trials, biostatistics, nephrology and intensive care, was established. The committee was located in the United Kingdom and was charged with reviewing unblinded data on patient characteristics, treatment compliance and study outcomes at regular intervals during the study, monitoring total mortality and serious adverse events, and making recommendations based on other outcomes such as cause-specific death or serious nonfatal adverse events.

Organization and Collaboration

The study is being conducted under the auspices of the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG) and the George Institute for International Health (GI), University of Sydney. It is overseen by a study management committee comprising principal and associate investigators. The coordinating and administrative center for the project is the

George Institute. The ANZICS CTG and the George Institute have demonstrated ability to conduct such large-scale, multicenter clinical trials [18, 19].

Patient Recruitment

The trial has been recruiting from all centers since early 2006. Site investigators have now randomized more than 900 patients and recruitment is proceeding at close to the predicted rate (fig. 1). On current randomization rates, it is expected that recruitment will be completed by early October 2008.

Outcomes and Significance

This study will provide high-quality evidence about the comparative effects of different targets for CRRT dose in patients with ARF treated in the Australian and New Zealand intensive care setting. This evidence will have direct relevance to decisions about the care of critically ill patients admitted to ICUs. If the study confirms the treatment effect reported in the *Lancet* study, augmented dose CRRT should become the standard of treatment in Australia, New Zealand and worldwide.

The Context

This study must be seen within the broader issues surrounding RRT. They include choice of therapy and dose [20–23], the epidemiology of dose selection [23, 24], the best approach to dose calculation [24–28] and the debate concerning dose selection and modality selection [29, 30]. Finally, it must seen in relation to the recent release of the results of the VA/NIH ARF trial [31]. Although a detailed discussion of these various aspects of RRT and the controversies that surround them is beyond the scope of this paper, we contend that, especially in view of the limitations of the VA/NIH ARF trial (late intervention, limited dose separation between high-dose IHD and low-dose CRRT, multiple modalities being applied to each patient, randomization after a period of up to 24 h of uncontrolled RRT in 64% of patients, high rate of non-recovery), the RENAL study will have significant and pivotal value of the intensive care and nephrology communities.

Conclusion

We have designed and are conducting a multicenter, randomized controlled trial of augmented dose RRT. Strong supportive evidence suggests this will reduce mortality, however, such therapy has not been widely adopted. We have addressed a variety of ethical, organizational, logistic and technical issues. If proven to decrease mortality, the proposed therapy would be highly cost-effective. This study is of great clinical and scientific importance and has the potential to save 15,000 lives per year worldwide.

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Appendix

The RENAL study is a collaboration of the Australian and New Zealand Intensive Care Society Clinical Trials Group and George Institute for International Health.

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Chapter 3

Renal replacement therapy for acute kidney injury in Australian and New Zealand intensive care units: a practice survey

Renal replacement therapy for acute kidney injury in Australian and New Zealand intensive care units: a practice survey

The RENAL Study Investigators

ABSTRACT

Background: There are few published data on the practice of renal replacement therapy (RRT) in Australian and New Zealand intensive care units. These data are essential for designing trials to compare new treatment approaches with "standard care".

Design: A prospective survey of RRT practice in ICUs interested in participating in the Australian and New Zealand Randomised Evaluation of Normal vs. Augmented Level (RENAL) Replacement Therapy in ICU Trial.

Setting and participants: 34 ICUs in Australia and New Zealand.

Outcome measures: Information on choice of therapeutic modality, technique, dose prescription, dose adjustment, technology, and replacement fluid composition before the initiation of the trial.

Results: All ICUs used continuous veno–venous RRT (CRRT) as the therapy of first choice. The most common technique, continuous veno–venous (CVV) haemodiafiltration, was used in 62% (21/34) of ICUs, followed by CVV haemofiltration in 35%, (12/34) and CVV haemodialysis in 3% (1/34). Replacement fluid was given pre-filter (pre-dilution) in most cases (94%). Lactate-based replacement fluid or dialysate accounted for 55% of all commercial fluid supplied by pharmacies to participating ICUs, bicarbonate-based fluid for 43% and citrate-based fluid for 2%. In all ICUs, CRRT was prescribed by critical care physicians alone, according to unit policy. The effluent dose varied from 1.5 L/h to 4 L/h, and was not adjusted to body weight in any of the ICUs surveyed. The median (and mode) effluent dose was a fixed regimen of 2 L/h. The most commonly used machine was the Gambro Prisma (38%), followed by the Gambro AK 10 blood module combined with volumetric fluid infusion pumps (29%), and the Kimal Hygieia (18%). The median (and mode) blood flow was 200 mL/min. Given the information supplied on pre-dilution rates, the median blood flow, and estimates of haematocrit and body weight based on previous surveys, the "typical" prescribed CRRT urea clearance dose ("standard") before the RENAL trial was estimated to be approximately 25 mL/kg/h.

Conclusions: These findings provide insight into RRT practice in ICUs in Australia and New Zealand, as well as useful data to assess whether the control group in the RENAL trial receives "standard" therapy as delivered in Australian and New Zealand trial centres at the time.

Crit Care Resusc 2008; 10: 225–230

There are limited data on the current practice of renal replacement therapy (RRT) in Australian and New Zealand (ANZ) intensive care units. Studies conducted in the state of Victoria and in Australia in the mid-1990s[1,2] showed that continuous RRT (CRRT) was the dominant modality of treatment for ICU patients with acute kidney injury, and that most CRRT prescription was by critical care physicians. These studies reported limited information on RRT technique, and no information on the dose of CRRT prescribed or comparisons with national or international practices.

Data from the United States and Canada covering the same period indicated that practice in those countries clearly differed from ANZ practice, with intermittent haemodialysis (IHD) being the most common modality, and nephrologists the most common prescribing specialists.[3,4] These survey data were more recently confirmed in a multicentre US study.[5] The use of slow extended daily dialysis (SLEDD) was uncommon. Again, as in the ANZ studies, no information was provided on the dose of RRT prescribed.

An international survey conducted in 2004[6] obtained some information on dose, but these data were confined to patients with sepsis and acute kidney injury. More recently, a US survey involving all centres participating in the Veterans Affairs/National Institutes of Heath (NIH) Acute Renal Failure Trial Network (ATN) study, obtained information on modality, technique and dose of RRT from clinicians, to establish normative data for a study control group.[7] The investigators confirmed that IHD was the dominant RRT modality, and that dose was rarely adjusted to body weight. They estimated that the "average" prescribed dose corresponded to a weight-based dose of 20–25 mL/kg/h. This dose was similar to that recently reported in an international study of more than 50 ICUs in 24 countries,[8] and demonstrated that the results of a randomised controlled trial of CRRT dose published in 2000[9] have not been widely adopted into clinical practice.

A large-scale study to determine the optimal dose for CRRT was designed in 2004 by ANZ critical care researchers of the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS

Table 1. Survey questions asked of ICU directors

- Who prescribes RRT in ICU patients with AKI?
- Which RRT modality does your unit use as treatment of first choice in critically ill patients with AKI?
- Is RRT prescription practitioner-dependent or based on unit protocol?
- If CRRT is the therapy of choice, what is the technique of choice?
- If replacement fluid was given, where in relation to the filter was it given (before the filter or after the filter)?
- What RRT machines do you use for CRRT?
- What is the typical pump blood flow during CRRT in your unit?
- What is the typical dialysate flow rate during CRRT?
- What is the typical replacement fluid flow rate during CRRT?
- Is the dose of RRT the same for all patients or is it adjusted to body weight?
- What is the replacement fluid/dialysate buffer typically used in your unit?

RRT = renal replacement therapy. AKI = acute kidney injury. CRRT = continuous renal replacement therapy.

CTG) and George Institute for International Health. The study — the Randomised Evaluation of Normal vs. Augmented Level (RENAL) Replacement Therapy Trial — is a multicentre, randomised, controlled trial in critically ill patients with acute kidney injury that compares CRRT at an effluent dose of 25 mL/kg/h versus 40 mL/kg/h. In the absence of robust data about "average current clinical practice" in ANZ, the appropriate dose for the control arm of the trial was unclear. To obtain information on current clinical practice in the ICUs planning to participate in the RENAL trial, we conducted a survey of renal replacement therapy practice in those ICUs.

Methods

Directors or principal investigators of ICUs interested in participating in the study were emailed a questionnaire in October 2004, requesting information on their practice (Table 1). After determining which ICUs used CRRT as the technique of choice, we obtained specific information from each ICU or their pharmacy detailing the amount of commercial fluid acquired in the preceding 6 months to establish current unit use of lactate, citrate or bicarbonate fluids in exact detail.

Estimation of urea clearance dose

To determine measure of the dose of RRT expressed as mL/kg/h, we estimated urea clearance using the above data on CRRT technique, published data on average body weight for a cohort of Australian patients treated with CRRT,[8] and published data on haemoglobin values in Australian ICU patients.[10]

The estimated urea clearance dose (U Cl) was calculated using Equation 1:

$$U\ Cl = [U_{effl}] \times Q_{effl} / [U_{fil}]$$

where $[U_{effl}]$ is the concentration of urea in the effluent (mmol/L), Q_{effl} is the rate of effluent generation (mL/min), and $[U_{fil}]$ is the concentration of urea in the blood within the filter (mmol/L).

This final variable can be calculated from Equation 2:

$$[U_{fil}] = [U_{pl}] \times [1 - Q_{rf}/Q_p]$$

where $[U_{pl}]$ is the urea concentration in plasma (mmol/L), Q_{rf} is the flow rate of the pre-filter replacement fluid (mL/min), and Q_p is the plasma flow into the filter (mL/min).

Q_p in turn can be calculated according to Equation 3:

$$Q_p = Q_b \times [1 - Htc]$$

where Q_b is blood flow into the filter set by the blood pump (mL/min), and Htc is the patient's haematocrit as a fraction of 1 (eg, haematocrit of 30% = Htc of 3).

Data analysis and presentation

Aggregate data are summarised using descriptive statistics. The choice of technique is presented as percentage of surveyed units using a given CRRT approach, as all data were unit-based rather than practitioner-based. Using this method, we describe the percentage of units using a specific technique of CRRT, the average volume of effluent generated, and the percentage use of pre-dilution. For CRRT machines, we present values as the percentage of all machines in use that belonged to a particular model. Finally, for the use of different fluids, we describe the percentage of each given fluid supplied by pharmacies to participating units over a 6-month period.

Results

We obtained information from 34 ICUs. An additional ICU, which joined the RENAL trial in 2006, was not surveyed.

All investigators reported applying protocols where all practitioners in that ICU prescribed RRT according to the agreed approach.

Type of renal replacement therapy

In all ICUs, the therapy of first choice was veno–venous CRRT, which was applied initially to all patients with acute kidney injury. This therapy was applied until recovery to independence of RRT, discharge or death to all patients in 23 of 34 units. In the remaining 11 units, IHD or SLEDD was occasionally prescribed in clinically selected patients (estimated as < 10%) who were haemodynamically stable and approaching ICU discharge. If IHD was applied, its prescription was left to the nephrology unit that would be responsible for the patient's renal condition after ICU discharge. If SLEDD was applied, it was typically under the prescription

Figure 1. Number of ICUs practising CRRT in each hourly effluent dose bracket in Australia and New Zealand

CRRT = continuous renal replacement therapy.

of the critical care physician, with unit protocols less strictly defined than for CRRT. No further details were obtained on IHD and SLEDD dose prescription.

Method of continuous renal replacement therapy

All ICUs used only veno–venous CRRT techniques. The most common technique was continuous veno–venous haemodiafiltration (CCVHDF), which was used in 21 ICUs (62%), followed by CVV haemofiltration (CCVH), which was used in 12 ICUs (35%), and CVV haemodialysis (CCVHD), which was used in one ICU (3%). When replacement fluid was used, it was delivered before the filter (pre-dilution) in 94% (32/34) of ICUs. The median reported blood flow during CRRT was 200 mL/min. When using CVVHDF, 91% (19) of ICUs reported delivering dialysate and replacement fluid at a ratio of 1 : 1.

Pharmacy reports revealed that lactate-based fluid accounted for 55% of all acquired commercial replacement fluid and dialysate, bicarbonate-based fluid for 43%, and citrate-based fluid for 2%.

The most commonly used CRRT machine was the Prisma (Gambro, Lund, Sweden) (38%, 13), followed by the Gambro AK-10 blood module combined with volumetric fluid infusion pumps (29%, 10), and the Hygieia (Kimal, Uxbridge, UK) (18%, 6). Where a Prisma machine was used, blood flow was prescribed at between 150 and 180 mL/min in all cases. Where a Prisma was not used (62%), blood flow of 200 mL/min was applied in all cases.

No ICU reported dosing CRRT according to patient weight. All used a fixed-dose regimen; the fixed dose was 2 L/h of effluent generation in 62% of ICUs, with this value ranging from 1.5 L/h to 4 L/h (Figure 1). The average effluent dose in ANZ trial centres was 2280 mL/h, typically delivered in CVVHDF mode with a dialysate to replacement fluid ratio of 1 : 1, and pre-filter delivery of replacement fluid, in the setting of a typical blood flow of 200 mL/min.

Urea clearance dose

We used the above information and estimates of body weight (80 kg) and haematocrit (0.25) to calculate the approximate typical weight-adjusted urea clearance dose delivered in ANZ before the RENAL trial. This was calculated to be 24.3 mL/kg/h.

Discussion

This survey of RRT practice in 34 ANZ hospitals participating in the RENAL trial had several important findings. First, in all centres, the therapy of choice at the time of trial inception was CRRT, with very limited use of IHD or SLEDD, which were typically delivered in the subacute phase before ICU discharge. Second, it was not practice to adjust dose according to body weight. Third, CVVHDF was the technique of CRRT most commonly used, typically using pre-filter fluid replacement in a ratio of dialysate to replacement fluid flow rate of 1 : 1. Fourth, prescribed blood flow rate varied from 150 to 200 mL/min, with 200 mL/min being the most commonly prescribed rate. Fifth, pharmacy-supplied fluids contained lactate as buffer in 55% of cases, bicarbonate in 43%, and citrate in 2%. Finally, we were able to estimate a likely "average" weight-adjusted urea-clearance equivalent dose before trial initiation and found it to be close to 25 mL/kg/h.

Our finding that CRRT is the treatment of choice applied to all patients at the start of RRT in all ICUs contrasts starkly with the recently published pre-trial findings of the US Veterans Affairs/NIH ATN study.[11] The latter reported that IHD was the most common RRT modality applied to the treatment of critically ill patients with acute kidney injury in 27 academic university-affiliated and veterans affairs medical centres in the US. Moreover, we found that the prescription of RRT was exclusively done by critical care physicians in ANZ, contrasting with nephrologists in the US, and that such prescription was based on unit-developed protocols in ANZ, contrasting with practitioner preference in the US. Finally, in contrast to US centres, ANZ centres did not use arterio–venous therapy. These differences in the prescription and practice of RRT in ANZ compared with the US are consistent with previous reports[1-4] and echo a long-standing and unresolved debate[12] on how best to treat critically ill patients with acute kidney injury. They also highlight the impossibility in ANZ of designing a dose study that is not fully based on the narrow concept of CRRT dose, rather than the broader concept of RRT dose. In this regard, it is likely that the Veterans Affairs/NIH ATN trial and the

RENAL trial may prove complementary in their findings, as they assess the issue of dose in two distinct health care contexts, with two different styles of practice. Together, these studies will greatly strengthen our knowledge of the effect of RRT dose on patient outcomes.

As in the US, ANZ clinicians do not adjust RRT dose to body weight. The reason remains unknown, but it highlights the need to know the average dose being used (in L/h) and the average weight of patients with acute renal failure (80kg) in order to design a trial that prescribes an "average weight-adjusted dose" to its control group. It is important to note several differences from the Veterans Affairs/NIH ATN trial survey in terms of the practice of CRRT. Although most of the CRRT in the US trial centres was conducted using CVVHD, only one ANZ centre used this technique. CVVHDF was the most common CRRT technique used in ANZ. The US centres also used CVVHDF commonly, and both US and ANZ centres used CVVH in about a third of patients.

Such use of CVVHDF and CVVH implies the administration of replacement fluid. Knowledge of the site of replacement fluid administration is important, as the average urea clearance dose ceases to be equivalent to the effluent dose when pre-filter fluid replacement is applied. Taking into account these factors, our survey revealed a self-reported effluent dose which was 25% higher than the mean self-reported "effluent dose" from the Veterans Affairs/NIH ATN trial investigators. These observations suggest that ANZ practitioners, while not prescribing CRRT on the basis of body weight or at the doses used in the study by Ronco et al,[9] appear to be delivering an average dose that is 25% higher than that delivered to the control group in the Ronco et al study.

When the average effluent dose was corrected for the effect of pre-dilution, blood flow, likely average haematocrit[10] and body weight,[8] the typical weight-adjusted urea clearance dose delivered in our trial centres was about 25 mL/kg/h. As recently argued in other trials of critically ill patients,[13] this finding suggests that, in the RENAL trial, control patients should receive this same dose using the CVVHDF technique and a dialysate to replacement fluid ratio of 1 : 1. This is representative of the control group treatment dose in the RENAL trial. However, in the RENAL trial, the practice of delivering replacement fluid in the pre-filter position was changed to avoid the solute dilution effect of such an approach. This effect would lead to greater solute dilution (and decreased urea and creatinine clearance) in the high-dose group compared with the low-dose group, and would significantly diminish the dose separation between the two treatments. Accordingly, it was agreed that post-filter replacement fluid administration was necessary.

The choice of fluids for replacement fluid and dialysate reported in our survey also differed from that reported in the US, with much less use of citrate-based fluids. We found that lactate-based fluids were used most commonly, but that use of bicarbonate was also quite common, representing 43% of all fluids used. Citrate-based fluids represented only 2% of total consumption. All ICUs used commercial fluids, with the same type of fluid used for both replacement fluid and dialysate. The nature and concentration of the buffer can have profound effects on acid–base balance; in particular, lactate-based fluids given at high dose can induce hyperlactataemia.[14] This effect would have led to a differential impact on blood lactate between the two study groups and generated a major confounder. Accordingly, it was agreed that in the RENAL study, all patients should receive CVVHDF using bicarbonate-based fluids with an identical concentration of bicarbonate.

Our study has both limitations and strengths. The accuracy of the responses to the survey could not be independently verified, and the description of CRRT practice was self-reported rather than an observation of actual practice. However, there was no reason for ICUs not to report their practice as accurately as possible, and an approach based on self-report was also used by the Veterans Affairs/NIH ATN study. The estimate of the typical prescribed dose relies on assumptions concerning likely mean haematocrit and body weight. However, as we used previously acquired and published data from ANZ ICUs,[8,12] these estimates are likely to approximate the actual value in the population under study. In addition, if the mean haematocrit was 0.3 rather than 0.25, the estimated dose would decrease by only 1.65 mL/min. Information obtained as part of the RENAL trial will confirm or refute the accuracy of our assumptions. We did not obtain specific information on the prescription of IHD and SLEDD as we estimate, from the responses obtained, that patients in ANZ ICUs spend < 5% of their RRT time receiving a therapy other than CRRT. In contrast to other studies of RRT practice, our study obtained verifiable data (from hospital pharmacies) on the type of commercial fluids used, which gave us a precise estimate of fluid choice and amount.

In conclusion, we surveyed self-reported practice in RENAL trial centres before the start of the trial to ensure that the dose to be delivered in the control group of the trial was consistent with existing standard therapy. These valuable data tell us much about current dialysis treatment for acute kidney injury in ANZ ICUs, as well as confirming that the treatment given to the lower-dose group in the RENAL trial is consistent with standard ANZ practice.

Table 2. The RENAL Study Investigators

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Chapter 4

Screening and Study Enrolment in the Randomized Evaluation of Normal vs. Augmented Level (RENAL) Replacement Therapy Trial

Original Paper

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Screening and Study Enrolment in the Randomized Evaluation of Normal vs. Augmented Level (RENAL) Replacement Therapy Trial

The RENAL Replacement Therapy Trial Investigators

Key Words
CONSORT statement · Continuous renal replacement therapy · Renal replacement therapy · RENAL Trial · VA/NIH ATN study

Abstract
Background and Objectives: Aspects of trial design, screening and study efficiency can affect recruitment and the findings of the trial itself. A clear understanding of the screening and study inclusion process will assist clinicians in interpreting trial results. ***Design:*** Prospective observational data collection on all patients screened for possible inclusion in a randomized controlled trial of normal vs. augmented renal replacement therapy in critically ill patients (the RENAL Trial). ***Setting:*** 35 hospitals in Australia and New Zealand. ***Participants:*** All patients screened for the RENAL Trial. ***Results:*** We screened 4,551 patients. Of these patients, 767 were ineligible because of lack of inclusion criteria and 2,085 because of exclusion criteria. Of the remaining 1,699, 1,508 (88.7%) were enrolled. The three most common exclusion criteria which prevented recruitment of potentially eligible patients were that the patient had end-stage kidney failure and was already on chronic dialysis (484; 23.2%), the patient's body weight was either <60 or >120 kg (456; 21.8%), and the fact that the patient had already received renal replacement therapy during the index admission. Important modifiable impediments to recruitment were inability to obtain consent in 191 cases, unavailability of research staff in 124 cases, physician objection in 89 cases, and inability to deliver the trial protocol in 78 cases. ***Conclusion:*** The RENAL Trial's enrolment efficiency was high and compared favourably with previous large intensive care units trials and with that of trials in patients with acute renal failure. The high rate of enrolment suggests that the results can be applied with confidence to most patients with de novo acute renal failure. The loss of close to 1.5% of patients due to consent issues highlights a common problem in critical care trials. The low rate of physician objection suggests clinical equipoise.

Introduction

Aspects of trial design, screening and study efficiency can affect enrolment, diminish representativeness, affect external validity, introduce selection bias and have a profound impact on the findings of the trial itself by either increasing or diminishing the treatment effect [1]. Such distortion of results may result in controversy, confusion and misinformation [1]. In particular, the representative-

The RENAL study is a collaboration of the Australian and New Zealand Intensive Care Society Clinical Trials Group and George Institute for International Health, see also Appendix.

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ness of the study sample is important in establishing the external validity of trial findings. This aspect of trial reporting, however, is often omitted, ignored or not clearly presented in the final manuscript [2, 3].

The Consolidated Standards of Reporting Trials (CONSORT) statement sets standards for improved reporting of clinical trials and recommends the presentation of details of exclusion criteria and quantification of their effect upon enrolment [4]. A cumulative, detailed and quantitative assessment of the reasons for exclusion of potentially eligible patients based on pre-specified criteria and a clear description of the reasons for failed enrolment of fully eligible patients offers important information about the external validity, representativeness, and robustness of the trial findings.

In keeping with the above recommendations, the investigators of the Veterans Affairs/National Institutes of Health (VA/NIH) Acute Renal Failure Trial Network (ATN) study, a multicenter randomized controlled trial in critically ill patients with acute kidney injury recently published a detailed report of the study's enrolment rate and provided information on the reasons for exclusion using a screening log [5]. This publication provided a benchmark for transparency and a unique opportunity to compare its screening and recruitment process with those of a similar study conducted in Australia and New Zealand. The study, called the Randomized Evaluation of Normal vs. Augmented Renal Replacement Therapy Trial (the RENAL Trial), assessed the effect of two doses of continuous renal replacement therapy (CRRT) on mortality in critically ill patients with acute kidney injury. As part of this study, we quantified the enrolment rate and reasons for exclusion using a screening log, thus giving us the ability to assess the external validity and representativeness of patients randomly assigned to the trial treatments and to compare such aspects of trial execution to those reported by the VA/NIH ATN study investigators.

Methods

Detailed descriptions of the background to and design of the RENAL study have been previously published [6, 7]. In brief, the RENAL study compared a less intensive (25 ml/kg/h) with a more intensive (40 ml/kg/h) dose of continuous veno-venous hemodiafiltration in critically ill patients with acute renal failure. The primary study outcome was 90-day all-cause mortality. A screening log of all patients evaluated for enrolment in the study was compiled monthly by research coordinators at each participating hospital. The log recorded all patients screened and either the reason patients were excluded or the reasons eligible patients were not enrolled. The data-coordinating center compiled a cumulative screening log monthly, using information from each hospital.

Table 1. Inclusion and exclusion criteria for RENAL

Inclusion criteria
- The treating clinician believed that the patient required CRRT for acute renal failure
- The treating clinician is uncertain about the balance of benefits and risks likely to be conferred by treatment with higher intensity or lower intensity CRRT
- The treating clinician anticipates treating the patient with CRRT for at least 72 h
- The patient fulfils at least one of the following clinical criteria for initiating CRRT:
  - Oliguria (urine output <100 ml/6 h) unresponsive to fluid resuscitation measures
  - Hyperkalemia ($[K^+]$ >6.5 mmol/l)
  - Severe acidemia (pH <7.2)
  - Plasma [urea] >25 mmol/l (BUN of 70 mg/dl)
  - Serum [creatinine] >300 μmol/l (3.4 mg/dl)
  - Clinically significant organ edema (e.g. pulmonary edema) in the setting of ARF

Exclusion criteria
- Age <18 years
- Death is imminent (<24 h)
- There is a strong likelihood that the study treatment will not be continued in accordance with the study protocol
- The patient has been treated with CRRT or other dialysis previously during the same hospital admission
- The patient was on maintenance dialysis prior to the current hospitalization
- The patient's body weight is <60 or >100 kg (amended to >120 kg after recruitment of 700 patients)
- The patient has been previously randomized to RENAL
- There is another major illness that, in the investigator's judgment, would substantially increase the risk associated with the subject's participation in the study

Screened patients were considered for enrolment if the treating clinician believed that the patient required CRRT for acute renal failure and the patient met one of the inclusion criteria and none of the exclusion criteria (table 1).

Patients who met all inclusion and no exclusion criteria constituted the fully eligible cohort. Fully eligible patients were not enrolled when they or their proxies were unwilling to provide informed consent or were unable to provide informed consent and the ethics committee did not approve the patient's participation into the study without prior informed consent. In 25 centers, however, delayed consent was approved. The enrolment rate was calculated as the ratio of enrolled and randomly assigned patients to fully eligible patients. Potentially eligible patients who met all inclusion criteria were evaluated for reasons for non-enrolment. The more frequent reasons for non-enrolment were broadly categorized in clusters and the percentage of potentially eligible patients who were excluded for each reason was determined.

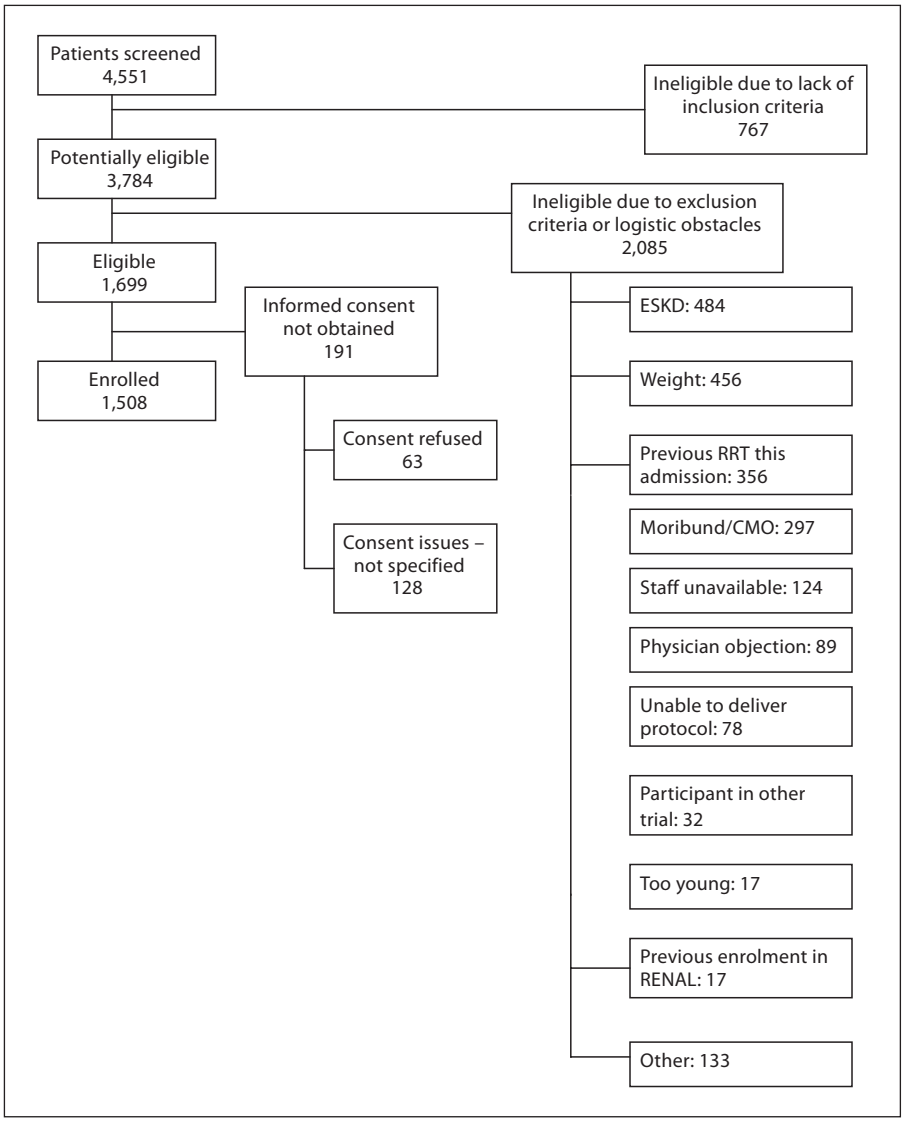
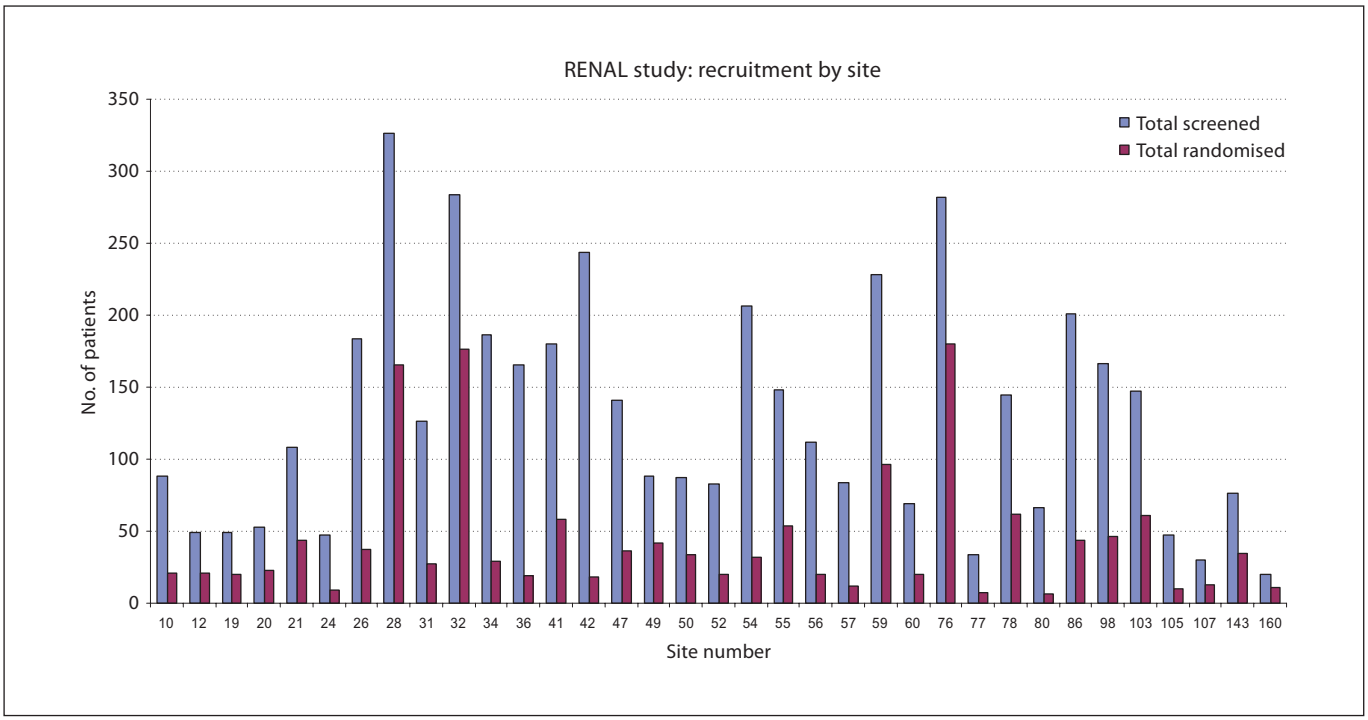


Fig. 1. Flow diagram describing the screening and enrolment process and the reasons for patient exclusion from enrolment.

Results

During the 33-month study enrolment period, 4,551 patients were screened. Of these potentially eligible patients, 767 were ineligible due to the lack of one or more inclusion criteria (fig. 1). Of the remaining 3,784 potentially eligible patients, 2,085 (55.1%) were ineligible as a result of the presence of one or more exclusion criteria. Of the remaining 1,699 fully eligible patients, 1,508 were enrolled, representing an enrolment rate of 33.1% of all patients screened and the inclusion of 88.7% of fully eligible patients into the trial. The enrolment numbers according to site are presented in figure 2.

Inability to obtain consent was a significant impediment to enrolment with a total of 191 patients excluded because of inability to obtain consent, representing 5% of potentially eligible patients and 11.2% of the fully eligible cohort. Other modifiable factors that were important barriers to enrolment were unavailability of research staff in 124 cases (3.3% of potentially eligible patients), physician objection in 89 cases (2.3% of potentially eligible patients), and inability to deliver the trial protocol in 78 cases (2.1% of potentially eligible patients). Involvement in competing trials was a minor impediment involving only 32 cases (<1% of potentially eligible patients).



Color version available online

Fig. 2. Histogram illustrating patient recruitment according to site. Each site is designated by a code number on the X-axis and the number of screened and enrolled patients is represented by the histogram bars (light for screening, dark for enrolment). The number of patients enrolled is given on the Y-axis.

Among non-modifiable factors, the presence of end-stage kidney disease as the trigger for the initiation of renal replacement therapy (RRT) was the most common exclusion criterion. Weight-based exclusion because the patients was either <60 or >100 kg in weight proved to be a major impediment to enrolment by excluding 12% of potentially eligible patients.

The upper weight limit for exclusion from the trial was later (June 21, 2007) changed to 120 kg to assist with recruitment and to increase the representativeness, external validity, once participating centers had the capacity to deliver continuous veno-venous hemodiafiltration at a dose of 4.8 liter/h (40 ml × 120 kg/h) with updated RRT devices. This change in exclusion criteria resulted in a progressive increase in the number of patients randomized each month (fig. 3). A number of patients were excluded because they were either moribund or had treatment limitation orders in place (7.8% of potentially eligible patients). Other causes including technical issues, need for urgent RRT precluding time for consent, failure to recognize patient eligibility, and insufficient data to classify the problem collectively accounted for 3.5% of non-enrolment of potentially eligible patients.

Discussion

We conducted an assessment of the screening and enrolment process during the RENAL study, the largest (n = 1,508) multicenter randomized controlled study of RRT dose conducted to date. The aim of this report is to provide clinicians with a transparent and quantitative report of the process of patient screening and enrolment during the trial, the reasons for exclusion of potentially eligible patients and the reasons for non-enrolment of fully eligible patients, before final statistical analysis and publication of trial results. By providing such information, we believe that the final results of the trial can be more clearly interpreted. Furthermore, our report makes it possible for the process of screening and enrolment during the RENAL study to be compared to the same processes during the VA/NIH ATN study, the only other large-scale (n = 1,124) multicenter randomized trial of renal replacement dose reported so far. Such comparison should make the cumulative interpretation of the highest level of evidence available in the literature more informative.

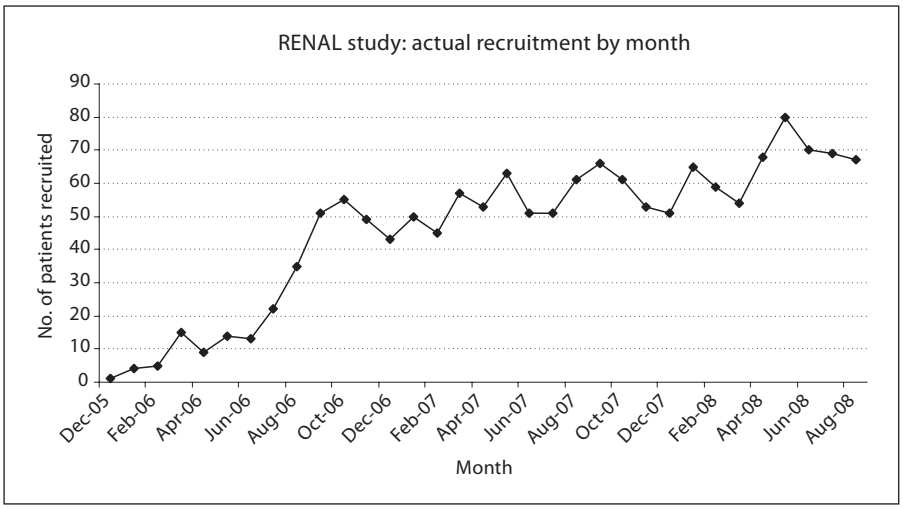


Fig. 3. Line graph representing monthly patient enrolment in the trial. Enrolment progressively increased with time.

We found that the number of screened patients in the RENAL study was remarkably similar to that reported by the VA/NIH ATN study investigators (4,551 in RENAL vs. 4,339 in VA/NIH ATN). However, from similarly sized screened cohorts the RENAL study was able to enrol more patients: 1,508 patients compared with 1,124 (33.2 vs. 25.9%) in the VA/NIH ATN trial, a relative increase in efficiency of 28.2%. The increased enrolment is probably due to a number of factors, most likely being the broader inclusion criteria with the inclusion of patients with acute and chronic kidney injury (but not patients with end-stage renal failure and already on chronic dialysis). As more centers participated in the RENAL study (35 vs. 22), recruitment was also faster at 45.7 patients/month compared with 25.5 patients/month in the VA/NIH ATN study.

A large proportion of screened patients in the RENAL study were not enrolled because they had one or more exclusion criteria that highlight a different screening process from that reported by the VA/NIH ATN study. For example, in the RENAL study, the application of RRT in the intensive care unit (ICU) to a patient with end-stage kidney disease triggered a screening procedure and exclusion in 484 potential patients (12.8%) compared with only 7.6% of patients being excluded because of CKD in the VA/NIH ATN study. These observations suggest some differences in both screening procedures and practice. They also highlight the increased number of patients with end-stage kidney disease treated with RRT in the ICU, a group of patients for whom only limited data exist [8, 9].

A significant portion of potentially eligible patients were also excluded on the basis of body weight. The RENAL study excluded patients with a pre-randomization weighing <60 kg because of the concern that the dose delivered to the low-dose group of patients (<1.2 liter/h) would have deviated too much from standard practice (typically 2 liter/h). No such group existed in the VA/NIH ATN study. The RENAL study also initially excluded patients with a body weight of >100 kg due to the fact that not all participating ICUs had RRT devices that could deliver the higher dose (defined as the production of 40 ml/kg/h of dialysate effluent) to such patients. The acquisition of RRT machines that could deliver a higher dose by most participating units during the course of the trial facilitated an increase in maximum allowed weight to 120 kg, a value similar to the 125 kg limit of the VA/NIH ATN study. This change increased the enrolment rate in the RENAL study. Given the initial weight limit of 100 kg, it is not surprising that the weight-based exclusion rate in the RENAL study was 12% of potentially eligible patients, twice the weight-based exclusion rate of the VA/NIH ATN study.

The recruitment efficiency of the RENAL study was high, with 33.1% of patients screened included and 88.7% of fully eligible patients enrolled. This level of efficiency compares favourably with the enrolment to screening and enrolment to fully eligible patients ratios in the VA/NIH ATN study (25.9 and 65.7%, respectively). It also compares favourably with several recent ICU trials, which reported these two key ratios at 29.2 and 64.7% [10], or reported enrolled to screened patients ratios of 10.2% [11] or 8.7% [12] or 4.3% [13]. However, many other recent key

ICU trials have not reported on their efficiency and/or representativeness [14–16]. In trials where information is presented on the number of screened patients and the number of patients enrolled in the trial, it is difficult to discern what percentage of the fully eligible patients who met the inclusion criteria and did not meet any exclusion criteria, were actually enrolled. A relatively high level of enrolment efficiency is beneficial from the point of view of cost, generalizability, representativeness and speed of execution. Unfortunately, no consensus terminology has evolved or is consistently applied in the reporting of such data.

A major barrier to the enrolment of otherwise fully eligible people was the inability to obtain consent. At 11.2% of such patients, the rate of refusal to consent to enrolment in the RENAL study was half that reported in the VA/NIH ATN study (21.4%), but still remained an area where efficiency can be improved. The principal reasons for the difference in refusal to consent between RENAL and the VA/NIH ATN studies remain unknown. Possible explanations include the fact that CRRT is the standard of care for acute kidney injury in Australian and New Zealand (ANZ) ICUs, the fact that the study simply altered the technical specifications of such therapy and the fact that intensive care specialists control CRRT prescription in ANZ. The need to initiate CRRT in the ICU would have made patient identification somewhat easier in such a system. Lack of availability of research staff accounted for the loss of another 3.2% of potentially eligible patients. This is similar to the reports of 'delayed notification of trial personnel' in the VA/NIH ATN study. Physician objection was low in the RENAL study at 2.3% of all eligible patients and similar to the 2.7% objection rate reported in the VA/NIH ATN study.

Among non-modifiable factors, 7.8% of exclusions were due to the patient being moribund or with limited life expectancy. This is very similar to the 11.8% value for this exclusion criterion reported in the VA/NIH ATN study. For other factors, comparability is not possible as the screening logs of the two trials reported on different exclusion criteria (previous RRT during the index admission, inability to deliver protocol, age, previous enrolment in the trial in the RENAL study vs. chronic illness and chronic kidney disease in the VA/NIH ATN study). For both studies, enrolment in a competing trial was a minor barrier to enrolment (<1% in the RENAL study and 2.3% in the VA/NIH ATN study).

Conclusions

Enrolment efficiency in the RENAL study compared favourably with other intervention trials in critically ill patients and with the VA/NIH ATN study conducted in a broadly equivalent population of critically ill patients. Such efficiency supports the representativeness and external validity of the RENAL study. Among modifiable factors, consent-related issues were a significant impediment to the enrolment of eligible patients. The selection of specific weight limits (both low and high) also significantly affected patient enrolment. Modification of the upper weight limit during the trial appeared to facilitate enrolment. A high level of acceptance of the trial protocol was confirmed by the low level of physician objection to enrolment, which strongly supported the validity of the premise of clinical equipoise in the conduct of the trial. The similarities in the screening process of the ATN and RENAL studies are striking and should facilitate subsequent individual patient data-based meta-analysis.

Appendix

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Chapter 5

The RENAL (Randomised Evaluation of Normal vs. Augmented Level of Replacement Therapy) study: statistical analysis plan

The RENAL (Randomised Evaluation of Normal vs. Augmented Level of Replacement Therapy) study: statistical analysis plan

Simon Finfer, Alan Cass, Martin Gallagher, Joanne Lee, Steve Su and Rinaldo Bellomo, on behalf of the RENAL Study Investigators

Contents

ABSTRACT

Background: The Randomised Evaluation of Normal vs. Augmented Level of Replacement Therapy (RENAL) study is the largest interventional trial ever conducted in patients with acute renal failure.

Objective: To develop and report a pre-determined statistical analysis plan which the investigators will adhere to in analysing the data from the trial.

Methods: The data collected by the researchers as part of the trial protocol was reviewed and formally assessed. Information relevant to baseline characteristics was selected and, for each item, statistically relevant descriptive elements were described. Information relevant to the process of care and delivery of prescribed trial therapy was similarly classified and, for each item, appropriate descriptive statistical analysis was planned with appropriate comparison between groups. Finally, trial outcomes were selected, and an appropriate statistical comparison between groups was planned and described.

Results: A standard analysis plan for the RENAL trial results was developed, which allows a comprehensive description of baseline characteristics, features of the process of care and trial treatment delivery, and pre-determined statistical assessment of relevant outcome measures in a way that is transparent, available to the public, verifiable and pre-determined before the actual analysis of data.

Conclusion: We have developed a pre-determined statistical analysis plan for the RENAL trial. This plan will be adhered to in order to avoid introducing any analysis bias associated with prior knowledge of study findings.

Crit Care Resusc 2009; 11: 58–66

1 Introduction

1.1 Study overview

The RENAL study described below is approaching completion, and represents a major research project by the Australian and New Zealand Intensive Care Society Clinical Trial Group (ANZICS CTG) and the George Institute of Interna-

tional Health. As part of a desire to maximise scientific rigour and transparency of analysis and to minimise any data manipulation, the RENAL Study Management Committee has agreed to develop, formally agree to, and abide by a pre-published statistical analysis plan. The plan, as described below, has been developed to precede any knowledge of study results, and we hope it will represent yet another important step toward making trials conducted by the ANZICS CTG the best that they can be in terms of execution and academic quality.

1.1.1 Title

The Randomised Evaluation of Normal vs. Augmented Level of Replacement Therapy (RENAL) study is the largest interventional trial ever conducted in patients with acute renal failure. It is a multicentre, open-label, randomised controlled trial that compares the effects of two regimens of continuous renal replacement therapy (CRRT), targeting either a standard dose or a higher dose of continuous veno–venous haemodiafiltration (CVVHDF): 25 mL/kg/h of effluent generation versus 40 mL/kg/h of effluent generation.

1.1.2 Patient population

In previous studies[1,2] of CRRT control, the benefit of delivering a higher dose was shown in a broad population of adult patients with acute renal failure and, for this reason, this is the population we chose to study. However, we chose to exclude patients who are moribund and at imminent risk of death (brain death or cardiac standstill) on the basis that allocation to either study treatment is unlikely to alter the patient's outcome. In addition, because renal recovery was chosen as an outcome measure, we chose to exclude patients receiving long-term dialysis.

1.1.3 Inclusion criteria

- The treating clinician believes that CRRT is needed for acute renal failure (ARF).
- The clinician has equipoise with regard to the two treatments.
- Consent has been obtained.
- The patient fulfils at least one of the physiological criteria of ARF:[3]
  - Urine output < 100 mL/6 h.
  - Serum potassium concentration > 6.5 mmol/L.
  - pH < 7.2.
  - Serum urea concentration > 25 mmol/L.
  - Serum creatinine concentration > 300 μmol/L.
  - Clinically significant organ oedema in the setting of ARF.

1.1.4 Exclusion criteria

Patients will be excluded from the study if one or more of the following criteria are present:

- Age is less than 18 years.
- Death is imminent (cardiac standstill or brain death expected in less than 24 hours), and the treating clinicians are not committed to full supportive care. This should be confirmed by a documented treatment-limitation order that exceeds a "not-for-resuscitation" order.
- There is a strong likelihood that the trial protocol will not be continued.
- The patient has been treated with CRRT or any other form of dialysis during this hospital admission.
- The patient is receiving long-term dialysis.
- The patient's body weight is < 60 kg or > 120 kg.
- The patient has previously been enrolled in the study.

1.1.5 Objectives

The primary aim of the study is to compare the effects of the two regimens prescribed to deliver different doses of CVVHDF on 90-day all-cause mortality in intensive care patients with ARF requiring CRRT. The null hypothesis is that there is no difference in the relative risk of death between patients assigned to standard dose CVVHDF and those assigned to higher-dose CVVHDF.

1.2 Unblinding

Access to the interim data and results will be limited to members of the Data and Safety Monitoring Board (DSMB) and the statistician(s) in charge of writing the reports. The statistical analysis plan will be written by a statistician and the principal investigator, both of whom will be blinded to treatment allocations and study results until the final study results are released by the study statistician. Treatment allocations will be stored securely in a separate location for that purpose. Statistician(s) not involved in the writing of DSMB reports will remain blinded and work on dummy treatment until validation of their data analysis and computer instruction codes has been performed — this will be done in accordance with the Standard Operating Procedures of the George Institute for International Health.

1.3 Definition of efficacy variables

1.3.1 Definition of primary outcomes

The primary endpoint is all-cause mortality 90 days post-randomisation. As loss to follow-up is expected to be minimal, missing values will not be imputed.

1.3.2 Definition of secondary outcomes

The secondary outcomes will include:

- Survival time from randomisation to Day 90.
- Renal replacement dependence at Day 28 and Day 90.
- Renal replacement days from randomisation to Day 90.

- ICU days from randomisation to Day 90.
- Hospital days from randomisation to Day 90.
- Mechanical ventilation days from randomisation to Day 28.

1.3.3 Definition of tertiary outcomes

The tertiary outcomes will include:

- 28-day all-cause mortality.
- Place of death (in study ICU, elsewhere in study hospital, or outside study hospital).
- Incidence of new organ failure at any time during the study. (A new organ failure is defined as a post-baseline SOFA score > 2 in any domain where the baseline SOFA score in that domain was 0, 1 or 2).

1.4 Definition of safety variables

No specific adverse events have been described in association with higher-dose CVVHDF. However, it is conceivable that higher-dose CVVHDF might increase the risk of dialysis disequilibrium syndrome, hypophosphataemia and hypokalaemia.

The safety variables will include:

- Number and proportion of patients experiencing serious adverse events.
- Number and proportion of patients with suspected dialysis disequilibrium syndrome in each group.
- Number and proportion of patients with morning hypophosphataemia (morning serum phosphate concentration < 0.8 mmol/L) in each group.
- Number of episodes of morning hypophosphataemia in each group.
- Number and proportion of patients with morning hypokalaemia (morning serum potassium concentration < 3.5 mmol//L) in each group
- Number of episodes of morning hypokalaemia in each group.
- Episodes of arrhythmia (any rhythm other than sinus rhythm) in each group.
- Number of episodes of arrhythmia requiring treatment in each group.
- Number of episodes of arrhythmia causing haemodynamic instability in each group.

1.5 Analysis principles

- All analyses will be conducted on an intention-to-treat basis.
- Results for all randomised patients will be analysed in the group to which they were assigned regardless of protocol violations. The only exception will be patients where consent to use their data in the analysis is withheld or withdrawn.
- All tests are two-sided, and the nominal level of α will be 5%.
- All statistical analyses will be unadjusted except where indicated.
- Subgroup analyses will be carried out irrespective of whether there is a significant effect of treatment on the primary outcome.
- We will not impute missing values unless specified otherwise. We will report the number of observations used in the analysis.
- *P* values will not be adjusted for multiplicity. However, the outcomes are clearly categorised by degree of importance (primary to tertiary), and a limited number of subgroup analyses are pre-specified.

2 Design issues

2.1 Data collection and follow-up

The different stages of data collection and follow-up are summarised in Box 1.

Because of local legal considerations, patients or their legal surrogates may have an absolute right to request that their data be removed from the study database. As a result, there are potentially two datasets: the randomised patients, and the randomised patients who have data available. The latter is obtained after deleting the data for randomised patients who withheld or withdrew their consent and did not allow their data to be submitted or maintained in the database. Only the latter dataset can be used in the analysis.

2.2 Study design

The RENAL study is a multicentre, open-label, randomised, concealed controlled trial.

2.3 Treatment allocation

Eligible patients will be randomised to one of the two doses of CVVHDF using imbalance minimisation. Centralised randomisation will be achieved via a password-protected web-based program.

2.4 Study power

The study will assume a conservative 90-day mortality rate of 60% in the low-dose group. The study will also assume a conservative estimate for the relative reduction in mortality in patients of only 50% of that reported by Ronco et al[1] (ie, 14.5%) and a parallel absolute reduction in mortality of 8.5%. Based on these figures, a study of 1500 patients will have a 90% power of detecting an 8.5% absolute reduction

from a 90-day mortality of 60% in the low-dose group to 51.5% in the higher-dose group ($\alpha < 0.05$). Such a difference is clinically significant (number needed to treat = 12) and would likely lead to widespread change in the practice of CRRT in Australia, New Zealand and other countries.

2.5 Interim analyses

An independent Data and Safety Monitoring Board (DSMB), chaired by Professor Colin Baigent (University of Oxford, United Kingdom), will review unblinded data on patient characteristics, treatment compliance and study outcomes at two interim analyses when the primary outcome for about 500 and 1000 patients, respectively, are available, and at the final analysis. Recruitment will be reviewed during the trial at regular intervals, to be determined by the DSMB, which will generate terms of reference. The DSMB will be charged with informing the Study Management Committees if at any time there emerges:

- evidence beyond reasonable doubt of a difference between randomised groups in all-cause mortality; or
- evidence likely to change the practice of many clinicians already familiar with the available evidence about the trial interventions.

2.6 Consent-related issues and dataset analysed

Due to the specific nature of the study, informed prior consent from participants or legal surrogates is not always possible, and patients or their legal surrogates may be asked for delayed consent after randomisation. Two important situations can lead to the cessation of study treatment:

Box 1. Data collected at different stages of the study

Randomisation

Patient demographics and inclusion/exclusion criteria.

Form 1. Baseline

Source and date of admission to ICU,
Acute Physiology and Chronic Illness Evaluation III (APACHE III) score,
ICU admission diagnosis,
subgroup categories, operative or non-operative admission,
emergency or elective surgery,
presence or absence of "severe sepsis" and suspected site of infection,
pre-admission treatment with HMG-CoA reductase inhibitors (statins),
treatment with a statin at baseline,
whether this is a readmission to ICU,
Sequential Organ Failure Assessment (SOFA) scores (cardiovascular, respiratory, hepatic, renal and haematological),
pre-morbid serum creatinine concentration, pre-randomisation serum creatinine and urea concentrations,
treatment with mechanical ventilation.
Haematological variables: international normalised ratio, activated partial thromboplastin time, haemoglobin concentration, white cell count, platelet count.
Biochemical test results: serum sodium, potassium, chloride, bicarbonate, urea, creatinine, phosphate, albumin and magnesium concentrations,
arterial blood gas variables (pH, carbon dioxide, base excess, ionised calcium) and glucose concentration.

Form 2. Daily, Days 1–28

Each day while in ICU:
Daily volume of fluid infused as part of continuous renal replacement therapy (CRRT) (replacement fluid plus dialysate) and total CRRT effluent.
Number of hours of CRRT treatment.
CRRT machine used (make and model), number of filters used per day, anticoagulant treatment used, insertion of CRRT vascular access, site of CRRT vascular access catheter, brand, gauge and length of CRRT vascular access catheter.
If intermittent haemodialysis given: whether net fluid balance was positive; and, if so, net positive haemodialysis fluid balance;
whether fluid was removed from the patient, and, if so, net negative haemodialysis fluid balance.
Daily blood product use and volume of red blood cells, platelets, fresh frozen plasma, cryoprecipitate, 4% albumin solution and 20% albumin solution.
All morning haematological, biochemical and arterial blood gas variables as described for baseline.
Whether the patient had an arrhythmia (any cardiac rhythm other than sinus rhythm),
type of arrhythmia and treatment given; and whether the arrhythmia caused cardiovascular instability (defined by site investigator).
Treatment with angiotensin-converting enzyme inhibitors.
SOFA scores (cardiovascular, respiratory, hepatic and haematological domains), treatment with renal replacement therapy or mechanical ventilation,
type (enteral versus parenteral) and volume of nutrition administered (total non-protein calories, protein, carbohydrate, and lipid will be calculated from type and volume of enteral and parenteral nutrition administered), all fluids administered.
Urine output, recorded total blood loss, and recorded total loss of other fluids.

Form 3. 28-day summary

Vital status (alive or dead) at Day 28.
Place, date and proximate cause of death.
Treatment limitations and details.
Whether patient is still in ICU; if not in ICU, date of discharge from index ICU admission.
Whether patient is still in hospital; if not in hospital, date of discharge from index hospital admission, number of days in ICU and hospital.
Whether patient is still receiving study treatment; if not, date of cessation of study treatment.
Whether patient has been treated with any other form of renal replacement therapy; if so, whether this is still ongoing; if not, date of cessation of this treatment.
Type of consent obtained for inclusion in RENAL study.

Form 4. 90-day summary

Vital status (alive or dead) at Day 90.
Place, date and proximate cause of death.
Treatment limitations and details.
Whether patient is still in ICU; if not in ICU, date of discharge from index ICU admission.
Whether patient is still in hospital; if not in hospital, date of discharge from index hospital admission, number of days in ICU and hospital.
Whether patient is still receiving study treatment; if not, date of cessation of study treatment.
Whether patient has been treated with any other form of renal replacement therapy; if so, whether this is still ongoing; if not, date of cessation of this treatment.
Type of consent obtained for inclusion in RENAL study.

- A patient, next of kin or legal surrogate may withdraw consent; or
- They may refuse continuation of study treatment when delayed consent is sought (as opposed to withdrawing an existing consent).

In both cases, the study treatment will cease, and the patient will receive renal replacement therapy as prescribed by their treating clinicians. In this situation, specific consent is sought to continue study follow-up procedures and to use study data. If consent for use of data is withheld, that patient's data will be removed from the analysis, except for data related to randomisation (occurrence of randomisation and treatment assignment) and consent.

The efficacy and safety datasets comprise all patients randomised except those whose consent has been withdrawn or withheld. Refer to *Section 1.5, Analysis principles*.

2.7 Permanent discontinuation

The data of patients who withdraw or withhold consent to continued study treatment, but consent to the use of their data will be included and analysed on an intent-to-treat basis.

3 Statistical analysis

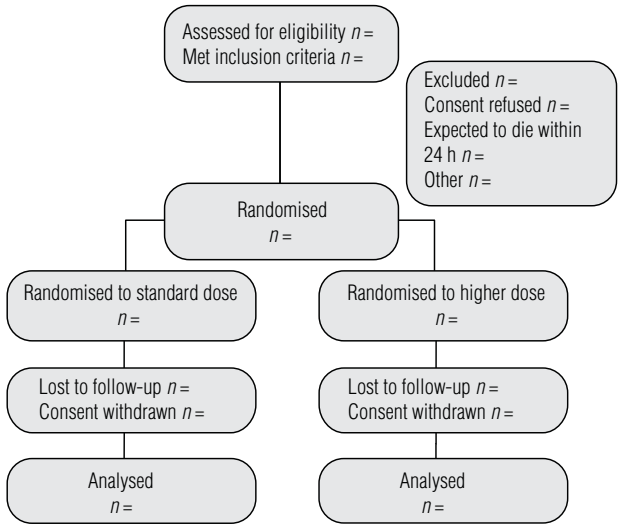
3.1 Trial profile

Flow of patients through the study will be displayed in a CONSORT diagram (Figure 1). We will report number of screened patients who met the study inclusion criteria and number included in the study, reasons for exclusion of those who met inclusion criteria, and information as below.

3.2 Characteristics of patients and baseline comparisons

Description of the following baseline characteristics will be presented by treatment group. Discrete variables will be summarised by frequencies and percentages. Percentages will be calculated according to the number of patients for whom data are available. Where values are missing, the denominator (which will be less than the number of patients assigned to the treatment group) will be stated in the corresponding summary table, in either the body or a footnote. In some instances, additional frequencies and percentage of patients in each category will be reported as indicated below. Continuous variables will be summarised by standard measures of central tendency and dispersion, using mean and standard deviation, as well as quantile points at 0.25, 0.5 and 0.75 where appropriate.

Figure 1. Flow of patients though the study



3.3 Baseline characteristics of patients

- Sex.
- Age.
- Weight.
- Percentage of patients with measured weight, percentage of patients with estimated weight, and method of weight estimation.
- Source of admission to ICU (emergency department, hospital floor, another ICU, another hospital, operating room [OR] following emergency surgery, OR following elective surgery, readmission to the same ICU during same hospitalisation).
- Operative or non-operative admission.
- Operative admission diagnosis (number and % in each of the following categories):
  - Cardiovascular
  - Respiratory
  - Gastrointestinal
  - Neurological
  - Trauma without traumatic brain injury
  - Traumatic brain injury ± multiple trauma
  - Burns
  - Renal
  - Gynaecological
  - Other orthopaedic
  - Other surgical.
- Non-operative admission diagnosis (number and % in each of the following categories):
  - Cardiovascular
  - Respiratory

  - Gastrointestinal
  - Neurological
  - Sepsis
  - Trauma without traumatic brain injury
  - Traumatic brain injury ± multiple trauma
  - Metabolic
  - Haematological
  - Burns
  - Renal
  - Other medical.
- Severe sepsis at baseline.
- APACHE III score.
- SOFA score:
  - Cardiovascular domain
  - Respiratory domain
  - Hepatic domain
  - Haematological domain.

  (SOFA score domains will be analysed both as continuous variables and as categorical variables divided into normal function (SOFA score, 0), dysfunction (score, 1–2), and failure (score, 3–4).
- Last serum urea concentration before randomisation.
- Last serum creatinine concentration before randomisation.
- Haematological variables (as described in Box 1).
- Biochemical variables (as described in Box 1).
- Treatment with mechanical ventilation.
- Estimated glomerular filtration rate (eGFR).
- Presence of an eGFR < 60 mL/min.

  The eGFR will be calculated using the revised modification of diet in renal disease (MDRD) equation:[4]

  $$eGFR = 175 \times (SCr \times 0.0113)^{-1.154} \times (age)^{-0.203} \times (0.742 \text{ [if female]})$$

  where SCr = serum creatinine level (μmol/L).

3.4 Process measures and concomitant treatments

Continuous variables will be summarised by standard measures of central tendency and dispersion, using mean and standard deviation, as well as quantile points at 0.25, 0.5 and 0.75 where appropriate. Discrete variables will be summarised by counts and percentages. The *t* test or Welch test will be performed in the case of continuous data, after checking for equality of variances using the Levene or Fligner–Killeen test. A non-parametric test, such as the Wilcoxon rank-sum test, will be used in case of small samples (< 30). Discrete data will be compared using the Pearson χ^2 test. In cases where the expected count is less than 1, the Fisher exact test or Fisher–Irwin test (the preferred option) should be used, and odds ratio and 95% CI reported instead.[5] For repeated measurements, *P* values will not be computed.

3.4.1 Process measures

- Days of study treatment.
- Days from cessation of study treatment to discharge from index ICU admission.
- Mean morning plasma urea concentration by day of treatment.
- Mean morning plasma creatinine concentration by day of treatment.
- Mean morning value for each biochemical variable (see Box 1) by day of treatment that is not already covered in the previous two items.
- Mean morning value for each haematological variable (see Box 1) by day of treatment
- Mean daily amount of effluent during study treatment.
- Mean daily amount of replacement fluid and dialysate during study treatment.
- Anticoagulant type, average treatment days received.
- Mean daily fluid balance during study treatment.
- Mean number of CRRT filters used daily during study treatment.
- Number of dialysis catheters used during study treatment.
- Mean daily urine output in mL.
- Number and percentage of patients treated with intermittent haemodialysis (IHD).
- Total number of treatments with IHD.
- Number and percentage of patients with a positive fluid balance during IHD.
- Number and percentage of patients with a negative fluid balance during IHD.

3.4.2 Concomitant treatments

- Non-protein calories administered in the ICU (by day, up to Day 14).
- Non-protein calories by all routes (by day, up to Day 14).
- Non-protein calories by enteral route (by day, up to Day 14).
- Non-protein calories by parenteral route (by day, up to Day 14).

  In the event that the number of patients remaining in the ICU becomes too small, the means will be truncated before 14 days. Conversely, the maximum of 14 days will be extended if more than 50% of patients remain in the ICU.
- Mean protein administration in g/day.
- Mean daily volumes of blood products while in ICU up to Day 28:
  - Red blood cells
  - Platelets
  - Fresh frozen plasma
  - Cryoprecipitate
  - 4% albumin solution
  - 20% albumin solution.

3.4.3 Limitation of treatment

For this section, only counts and frequencies will be reported.

- Patients for whom there was limitation of treatment.
- Patients for whom treatment was limited or withheld:
  - Patients for whom treatment was limited as terminal event.
  - Patients for whom maximal treatment was not indicated.
- Time from randomisation to first treatment limitation order (overall and for limitations indicated in specific study question in Day 90 study form).

Treatment limitation refers to withdrawing a treatment that might otherwise prolong life as it is no longer considered appropriate for that individual (ie, ceasing a previously provided treatment); or withholding treatment that might otherwise prolong life as it is not considered appropriate for that individual (ie, not commencing a treatment).

Each of these will have been authorised by a treating clinician independent of the study and documented in the medical record. The specific treatments limited or withdrawn will not be reported.

3.4.4 Consent and permanent discontinuation of study treatment

For this section, only counts and frequencies will be reported.

- Consent (number and % in each of the following categories):
  - Prior informed consent from patient.
  - Prior informed consent from a legal surrogate.
  - Delayed informed consent from patient.
  - Delayed informed consent from a legal surrogate.
  - Consent from other legal body before or after patient's death.
  - No consent obtained.
  - Consent withdrawn (no. and % of all consent obtained).
- Patients for whom study treatment permanently discontinued (number and % in each of the following categories):
  - Patient requested withdrawal.
  - Legal surrogate requested withdrawal.
  - Study treatment discontinued by treating clinician (not due to a serious adverse event or palliative care).
  - Study treatment discontinued due to serious adverse event.
  - Study treatment discontinued as focus of treatment changed to palliative care (derived from treatment limitation question on Day 90 form).
  - Study treatment discontinued for other reason.

3.5 Primary outcome

We will compare the difference in number and proportion of all-cause mortality at Day 90 between the two groups, using standard χ^2 tests, and a 95% confidence interval (CI) will be computed. Frequency and count for primary outcome per group will also be reported. A sensitivity analysis (assuming the best and worst possible case) will be performed if more than 5% of the 90-day mortality data are missing. A full logistic regression analysis examining the effect of treatment group, incorporating all the variables specified in the subgroup analysis below, might also be carried out, with or without transformation of variables, as necessary.

3.6 Secondary and tertiary outcomes

Survival time from randomisation to Day 90, duration of ICU stay and duration of hospital stay will be analysed using a log-rank test. The number of events and the median survival (if available) or event times or hazard ratio (including 95% CI) will also be reported. Kaplan–Meier curves will be used to display probability of survival or of experiencing an event, by treatment group. Survival times will be censored at the time when the patient was last known to be alive or to experience an event (for ICU or hospital discharge calculations). On the rare occasion that assumptions are needed as to the time patients were last known to be alive or to experience an event, they must be explicitly specified and consistently applied between treatment groups.

Renal replacement days up to Day 90, and mechanical ventilation days up to Day 28 will be analysed as continuous variables, without censoring, with reporting of mean and standard deviation, as well as quantile points at 0.25, 0.5 and 0.75. Comparison of differences in mean and median between the two groups will be carried out using the *t*/Welch or Wilcoxon rank-sum test, as outlined in *Section 3.4*.

A standard χ^2 test and 95% CI testing the difference in proportion between two treatment groups will be used to assess the effect of treatment on binary or categorical outcomes (ie, 28-day all-cause mortality, cause of death, place of death, renal replacement dependence at Day 28 and Day 90, incidence of a new organ failure at any time since baseline [from no failure up to five failures]). In case of an expected count less than 1, the Fisher exact test or Fisher–Irwin test (the preferred option) should be used, and odds ratio and 95% CI will be reported instead.

3.7 Safety outcomes

Safety outcomes as defined in *Section 1.4* will be analysed via frequencies and percentages per treatment group. The difference in proportions of patients experiencing a particular event (at least once) will be tested across treatment arm by means of a χ^2 or Fisher/Fisher–Irwin test. Additionally, the difference in number of episodes between treatment groups for morning hypophosphataemia (measured serum phosphate concentration < 0.8 mmol/L) at any time in the ICU will be compared using Welch, *t* or Wilcoxon rank-sum

tests, with 95% CI reported. The same will apply to episodes of morning hypokalaemia (serum potassium concentration < 3.5 mmol/L). Denominators for discrete variables are based on all patients randomised.

3.8 Subgroup analyses

All subgroups will be defined by the presence or absence of a pre-randomisation variable; we will not select any subgroups based on post-randomisation events.

The primary outcome for planned subgroup analyses will be the same as for the main analysis: 90-day all-cause mortality.

3.8.1 Analysis

The main analysis for each subgroup will be a test of interaction in a logistic model to determine whether the effect of treatment differs significantly across categories (eg, in patients with sepsis versus those without sepsis). Odds ratio and 95% CI for each category will be reported, as well as the *P* value for the interaction test.

We will conduct subgroup analyses for patients with the following baseline characteristics:

- Patients with severe sepsis versus those without severe sepsis.
- Patients with at least one non-renal failing organ versus those with single (kidney) organ failure.
- Patients with SOFA cardiovascular score of 3–4 versus those with a SOFA cardiovascular score of < 3 at baseline.
- Patients with known premorbid chronic renal disease (pre-admission eGFR < 60 mL/min, using MDRD equation) versus those with premorbid eGFR ⩾ 60 mL/min.

3.8.2 Rationale

The rationale for considering these subgroups is as follows. Patients with sepsis, multiorgan failure, vasopressor requirements or premorbid renal dysfunction have been reported as potentially having different outcomes and responses to therapy, or have been studied separately in other major studies of CRRT or haemodialysis.[1,2,6-13] They are considered likely to differ in terms of clinical course and potential response to therapy from the populations in epidemiological studies.[14]

3.8.3 Presentation of results

Subgroup results for categorical variables will be presented as forest plots, with *P* values for heterogeneity (interaction test) for each pair of subgroups.

3.9 Control of type I error for multiple looks

The Haybittle–Peto rule with a maximum of three analyses will be used to control the overall type I error to 0.05. The critical value to be used for primary and secondary outcomes in our study is 1.975.

3.10 Tables and figures

Tables will include baseline characteristics of the participants (Table 1), process measures and concomitant treatments (Table 2), outcomes including safety outcomes (Table 3 and Table 4), and subgroup analyses (Table 5). Examples of the format of the tables are available at <http://www.thegeorgeinstitute.org/research/renal/studies/rct-of-normal-vs.-augmented-level-of-renal-replacement-therapy-in-icu---renal.cfm>.

Planned figures are:

- A CONSORT diagram illustrating the flow of patients through the study (Figure 1).
- A line graph for mean (95% CI) morning urea concentration by treatment group for the first 14 days.
- A forest plot of odds ratios for death at 90 days for all patients and for the a-priori subgroups described in *Section 3.8*.
- A Kaplan–Meier curve for survival to 90 days.

3.11 Future ancillary analyses

Although the primary analysis is as described above, we plan to use the data obtained from this study to conduct subsequent exploratory analyses. The goal of these post-hoc analyses is to detect specific associations between aspects of the processes of care and outcomes in all patients combined. Such exploratory analyses will be defined and described before execution, after the primary analysis has been completed, and the results of the primary study are published.

Acknowledgements

The statistical analysis plan was completed on 28 November 2008 and has been approved by the RENAL Study Management Committee.

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Rinaldo Bellomo, Principal Investigator, RENAL study, and Chair of Trial Management Committee[1,2]
On behalf of the RENAL Study Investigators (Box 2)

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Chapter 6

Intensity of Continuous Renal-Replacement Therapy in Critically Ill Patients

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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.

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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-

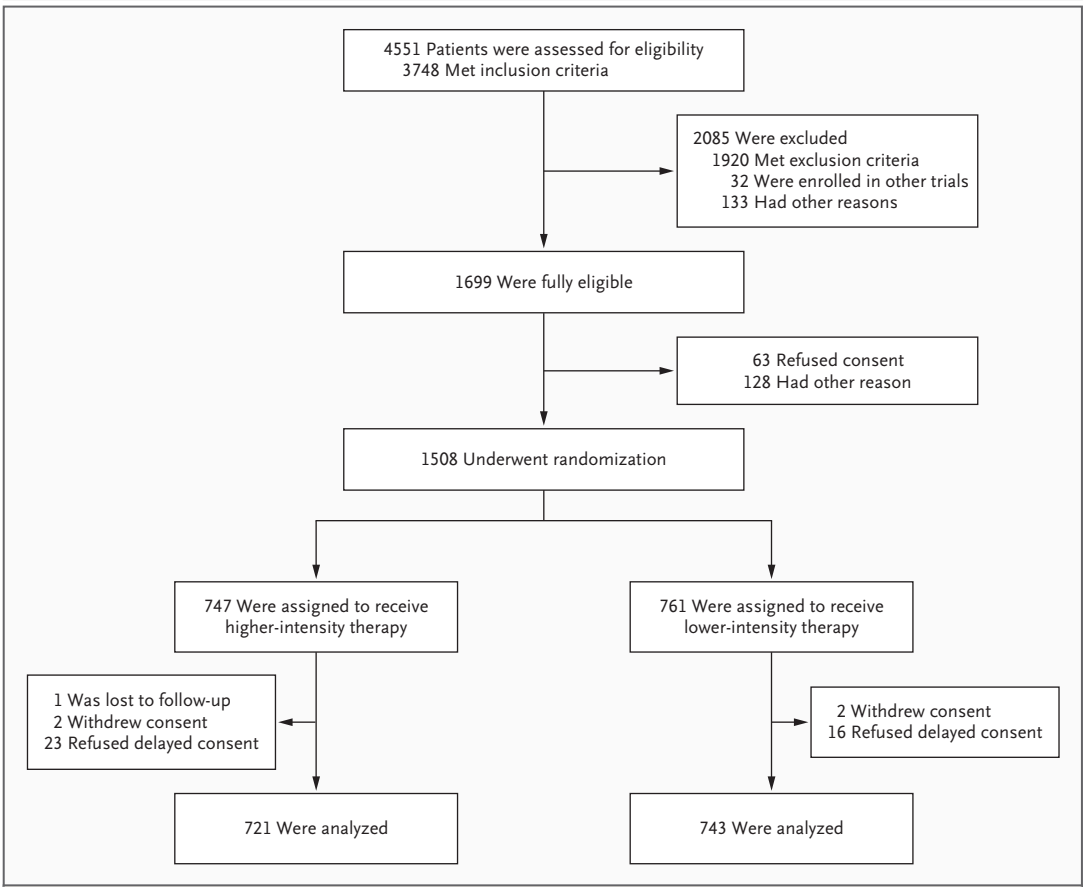

Figure 1. Numbers of Patients Enrolled in the Study, Randomly Assigned to a Treatment Group, and Included in the Analysis.

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-

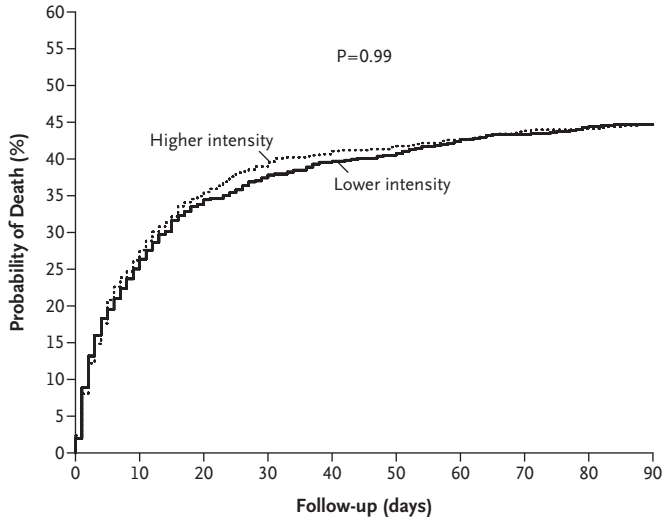

Figure 2. Kaplan–Meier Estimates of the Probability of Death.
Mortality at 28 days was similar in the higher-intensity and lower-intensity treatment groups (38.5% and 36.9%, respectively), and mortality at 90 days was the same (44.7%) in both groups.

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

Prespecified Subgroup	Higher Intensity (N=721)	Lower Intensity (N=743)	Odds Ratio (95% CI)
	no. of deaths/no. of patients (%)		
Patients with criteria for sepsis			
Yes	168/359 (46.8)	186/363 (51.2)	0.84 (0.62–1.12)
No	154/362 (42.5)	145/379 (38.3)	1.19 (0.89–1.60)
Patients with at least one nonrenal organ failure			
Yes	299/628 (47.6)	306/649 (47.2)	1.02 (0.82–1.27)
No	23/93 (24.7)	25/93 (26.9)	0.89 (0.46–1.72)
Patients with SOFA cardiovascular score of 3 or 4			
Yes	247/510 (48.4)	254/546 (46.5)	1.08 (0.85–1.37)
No	74/210 (35.2)	75/194 (38.7)	0.86(0.58–1.29)
Patients with eGFR <60 ml/min			
Yes	114/250 (45.6)	105/222 (47.3)	0.93 (0.65–1.34)
No	81/157 (51.6)	81/185 (43.8)	1.37 (0.89–2.10)
Missing	127/314 (40.5)	146/336 (43.5)	0.88 (0.65–1.21)
Death from any cause by day 90	322/721 (44.7)	332/743 (44.7)	1.00 (0.81–1.23)

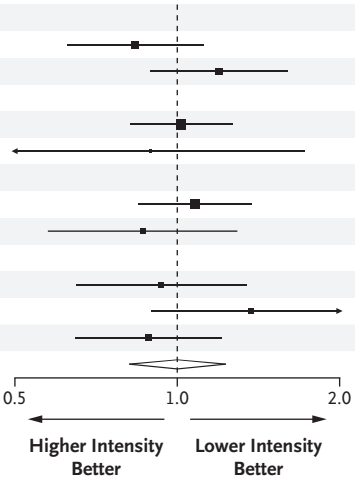

Figure 3. Mortality in the Prespecified Subgroups and among All Patients.

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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- contact information

Chapter 7

An observational study of fluid balance an patient outcomes in the randomized evaluation of normal vs. augmented level of replacement therapy trial

An observational study fluid balance and patient outcomes in the randomized evaluation of normal vs. augmented level of replacement therapy trial*

The RENAL Replacement Therapy Study Investigators

Objective: **To examine associations between mean daily fluid balance during intensive care unit study enrollment and clinical outcomes in patients enrolled in the Randomized Evaluation of Normal vs. Augmented Level (RENAL) replacement therapy study.**

Design: **Statistical analysis of data from multicenter, randomized, controlled trials.**

Setting: **Thirty-five intensive care units in Australia and New Zealand.**

Patients: **Cohort of 1453 patients enrolled in the RENAL study.**

Interventions: **We analyzed the association between daily fluid balance on clinical outcomes using multivariable logistic regression, Cox proportional hazards, time-dependent analysis, and repeated measure analysis models.**

Measurements and Main Results: **During intensive care unit stay, mean daily fluid balance among survivors was −234 mL/day compared with +560 mL/day among nonsurvivors ($p <$ .0001). Mean cumulative fluid balance over the same period was −1941 vs. +1755 mL ($p =$ .0003). A negative mean daily fluid balance during study treatment was independently associated with a decreased risk of death at 90 days (odds ratio 0.318; 95% confidence interval 0.24−0.43; $p <$ .000.1) and with increased survival time ($p <$ .0001). In addition, a negative mean daily fluid balance was associated with significantly increased renal replacement-free days ($p =$ .0017), intensive care unit-free days ($p <$ .0001), and hospital-free days ($p =$ .01). These findings were unaltered after the application of different statistical models.**

Conclusions: **In the RENAL study, a negative mean daily fluid balance was consistently associated with improved clinical outcomes. Fluid balance may be a target for specific manipulation in future interventional trials of critically ill patients receiving renal replacement therapy. (Crit Care Med 2012; 40: 1753–1760)**

Key Words: acute kidney injury; continuous renal replacement therapy; hemodialysis; hemofiltration; intensive care; kidney

Fluid resuscitation is considered beneficial in critically ill patients at risk for or with acute kidney injury (AKI) (1), and intravenous fluids are commonly administered to maintain adequate renal perfusion (2–4). This practice paradigm appears common and perhaps dominant in intensive care units (ICUs) worldwide (5–7).

The concept that liberal fluid administration is good for the kidney has been recently challenged (1, 5). Observational studies of patients with AKI have linked a positive fluid balance (FB) before or during renal replacement therapy (RRT) with increased mortality (9–15). More recently, an analysis of AKI patients from the ARDS Network trial of liberal vs. conservative fluid management in acute lung injury patients identified an independent association between positive FB and mortality (16).

The Randomized Evaluation of Normal vs. Augmented Level (RENAL) study (17–20) offers a unique opportunity to explore the association between FB. Accordingly, we conducted a secondary

***See also p. 1970.**

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The Randomized Evaluation of Normal vs. Augmented Level (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.

The members of the writing committee (Rinaldo Bellomo, MBBS, MD; Alan Cass MBBS, PhD; Louise Cole, MBBS, PhD; Simon Finfer, MBBS; Martin Gallagher MBBS; Joanne Lee, BMedSc (Hons); Serigne Lo, PhD, MSc, BSc; Colin McArthur, MBBS; Shay McGuiness, MBBS; Robyn Norton, PhD, MP; John Myburgh, MBBS, PhD; and Carlos Scheinkestel, MBBS) take responsibility for the content of this article.

The affiliations of the members of the RENAL Replacement Therapy Study writing committee and the names and affiliations of the Investigators are listed in the Appendix.

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analysis of the RENAL study data focusing on the relationship between FB and primary and secondary predefined study outcomes.

MATERIALS AND METHODS

The RENAL study was a multicenter, randomized, controlled trial (RCT) of intensity of continuous renal replacement therapy (CRRT) in 1508 critically ill patients with AKI (17). The Human Research Ethics Committees of the University of Sydney and all participating institutions approved the study.

The methodologic details of the RENAL study were recently reported (17). In brief, patients were eligible for enrollment if they were critically ill adults with AKI, were deemed to require RRT by the treating clinician, and fulfilled predefined criteria (urine output <100 mL/6 hrs unresponsive to fluid resuscitation or a potassium level >6.5 mmol/L or a pH <7.2 or a urea concentration >25 mmol/L or a creatinine level >300 μmol/L or clinically significant organ edema, e.g., lung). The presence of clinically significant organ edema was defined by clinician opinion. This included radiologically confirmed pulmonary edema or visible or palpable organ edema (cardiac or gastrointestinal) at surgery. Eligible patients were randomly assigned to continuous veno-venous hemodiafiltration with effluent flow at 40 mL/kg/hr (higher intensity) or 25 mL/kg/hr (lower intensity). Study treatment was discontinued on death, discharge from ICU, or recovery of renal function. The primary study end point was death from any cause by day 90.

Fluid Balance. FB and cumulative FB data were obtained using data from each study day after randomization until the occurrence of death, ICU discharge, or completion of 28 days from study randomization, whichever occurred first.

No FB data were obtained before randomization. However, clinicians were asked to identify whether a patient did or did not have clinically significant organ edema as described. Daily FB was calculated as the difference between fluid administered (intravenous fluids + blood products + enteral fluids + dialysate + RRT replacement fluids) and fluid lost (dialysis effluent from CRRT [when applied] + urine output + blood losses + enteral losses + drain losses).

A negative FB was present when fluid loss was greater than fluid administered (indicated by a negative sign) and a positive FB was present when fluid removal was less than fluid administered (indicated by a positive sign).

Mean daily FB was calculated for each day during ICU study enrollment. Incomplete study days (day of randomization and day of discharge or death) were considered full data collection days. FB was adjusted for body weight and also calculated as cumulative FB over the period of observation. We also assessed the relationship between FB and the cardiovascular Sequential Organ Failure Assessment (SOFA) score, renal SOFA score, and both albumin levels and albumin therapy.

Statistical Analysis. Continuous variables were expressed as means with SD for normally distributed variables and as median and interquartile range for non-normally distributed variables. Comparisons were made using Student *t* test or the Mann-Whitney test when appropriate. Categorical variables were expressed as proportions and compared with the chi-square test or Fisher exact test as appropriate.

Mean daily FB-related variables and all baseline variables (biochemical, demographic, clinical, and illness severity-related) were used to create a multivariate logistic regression model using mortality at 90 days as the dependent variable. Such models included a propensity score. The propensity score was estimated

Table 1. Baseline characteristics and outcome of patient with a mean daily positive vs. negative fluid balance

Baseline Characteristics	Positive Mean Daily Fluid Balance, n = 705	Negative Mean Daily Fluid Balance, n = 748	*p*
Age	64.5 (14.7)	64.7 (14.9)	.85
Male	446/705 (63.3%)	491/748 (65.6%)	.34
Estimated glomerular filtration rate	57.9 (32.7)	55.2 (29.4)	.21
Mechanical ventilation	548/705 (77.7%)	523/748 (69.9%)	<.001
Severe sepsis at baseline	371/705 (52.6%)	348/748 (46.5%)	.02
Acute Physiology and Chronic Health Evaluation III score	106.8 (26.7)	98.2 (24.0)	<.0001
SOFA cardiovascular	3.0 (1.5)	2.7 (1.6)	<.001
SOFA respiration (score)	2.8 (1.0)	2.7 (0.9)	.03
SOFA coagulation (score)	1.0 (1.2)	0.9 (1.1)	.08
SOFA liver (score)	1.0 (1.2)	0.9 (1.2)	.60
Weight	79.9 (12.9)	81.4 (12.9)	.03
Source of admission			.
Accident and emergency department	194/658 (29.5%)	152/701 (21.7%)	<.01[a]
Hospital floor/ward	182/658 (27.7%)	203/701 (29.0%)	—
Transfer from another intensive care unit	58/658 (8.8%)	53/701 (7.6%)	—
Transfer from another hospital	73/658 (11.1%)	79/701 (11.3%)	—
Admitted from operating theater/recovery after emergency surgery	88/658 (13.4%)	115/701 (16.4%)	—
Admitted from operating theater/recovery after elective surgery	63/658 (9.6%)	99/701 (14.1%)	—
Nonoperative admission diagnosis			—
Cardiovascular	298/531 (56.1%)	230/511 (45.0%)	.01[a]
Genitourinary	94/531 (17.7%)	135/511(26.4%)	—
Gastrointestinal	35/531 (6.6%)	40/511 (7.8%)	—
Hematology	14/531 (2.6%)	8/511 (1.6%)	—
Metabolic/endocrine	12/531 (2.3%)	13/511 (2.5%)	—
Neurologic	7/531 (1.3%)	4/511 (0.8%)	—
Respiratory	67/531 (12.6%)	78/511 (15.3%)	—
Transplant	3/531 (0.6%)	2/511 (0.4%)	—
Trauma	1/531 (0.2%)	1/511 (0.2%)	—
Operative admission diagnosis			—
Cardiovascular	111/174 (63.8%)	156/237 (65.8%)	.1260[a]
Genitourinary	2/174 (1.1%)	2/237 (0.8%)	—
Gastrointestinal	44/174 (25.3%)	54/237 (22.8%)	—
Neurologic	5/174 (2.9%)	2/237 (0.8%)	—
Respiratory	3/174 (1.7%)	5/237 (2.1%)	—
Transplant	0/174 (0.0%)	9/237 (3.8%)	—
Trauma	9/174 (5.2%	9/237 (3.8%)	—
Plasma urea (mmol/L)	22.9 (12.8)	23.8 (12.3)	.1323
Creatinine at randomization (μmol/L)	326.7 (214)	346.6 (202)	.0684
pH	7.2 (0.1)	7.3 (0.1)	<.0001
Bicarbonate (mmol/L)	17.5 (6.2)	19.1 (5.4)	<.0001
Base excess (mmol/L)	−29.3 (7.4)	−27.3 (6.4)	<.0001
Outcomes			
Number of renal replacement therapy-free days	15.1 (11.6)	19.7 (8.9)	<.0001
Number of intensive care unit-free days	37.2 (39.5)	60.4 (34.4)	<.0001
Number of hospital-free days	23.5 (31.6)	40.8 (33.2)	<.0001
Mechanical ventilation-free days	37.7 (39.5)	59.8 (36.0)	<.0001
Number of deaths at 90 days	403/705 (57.2%)	241/747 (32.3%)	<.0001

SOFA, Sequential Organ Failure Assessment.

Continuous variables expressed as mean with SD in brackets.

Nominal variables expressed as number with percentage in brackets. All values obtained at randomization.

[a]Value for overall comparison.

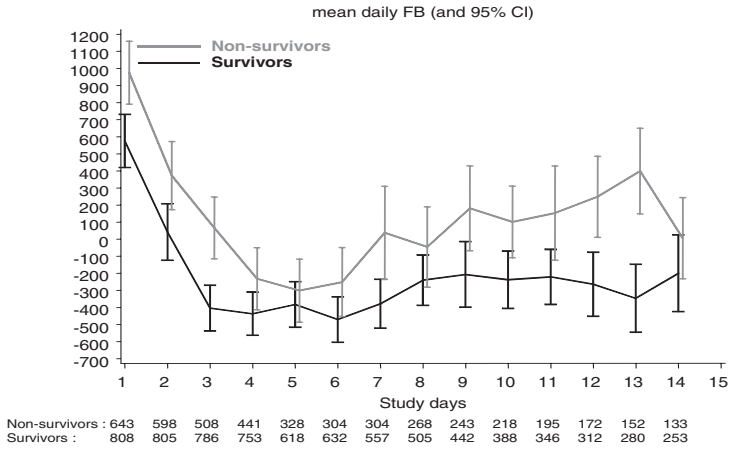

Figure 1. Graphic representation of mean daily fluid balance over the first 2 wks of observation after randomization according to survival status at 90 days (survivors = *continuous line*; nonsurvivors = *broken line*). The *y-axis* indicates mean daily fluid balance in mL/d. Mean daily FB during was significantly more positive in nonsurvivors. The *minus sign* indicates a negative fluid balance. For each study day on *x-axis*, the number of patients analyzed is also reported. The *vertical line* indicates the mean duration of renal replacement therapy at 6 days. *CI*, confidence interval.

by using a multivariate logistic regression of patients receiving positive mean daily fluid balance (MDFB) or not. The model included all available hospital characteristic variables in this study, such as country, region, and type of hospital. Patients are then divided into four strata based on the quartile of the estimated probabilities of receiving positive MDFB. This latter variable is included as covariate in the death at 90 days of analysis.

Multivariate linear regression analysis was used to assess the relationship between FB and mechanical ventilation-free days, RRT-free days, ICU-free days, and hospital-free days at 90-day follow-up as the dependent variables. Analysis of time to death within 90 days of randomization used the Kaplan-Meier product limit estimates and compared survival curves using the log-rank test.

To test the robustness of any association between mortality and FB, additional models were applied to data analysis. These models included time-dependent modeling, repeated measure modeling, and Cox proportional hazards modeling, all with adjustment with the following prespecified variables: treatment group, all Acute Physiology and Chronic Health Evaluation III diagnostic groups, daily use of CRRT, age, time from ICU to randomization, presence of sepsis, SOFA respiratory score, SOFA coagulation score, SOFA liver score, SOFA cardiovascular score, SOFA renal score, presence of nonrenal organ failure, international normalized ratio for prothrombin time, activated partial thromboplastin time, platelet count, serum creatinine, Pa_{O_2}/Fi_{O_2} ratio, Pa_{CO_2}, use of mechanical ventilation, and clinical diagnosis of significant edema at randomization.

A two-sided $p < .05$ was used to indicate statistical significance. Statistical analyses were performed and independently checked with the use of SAS software version 9.1.

RESULTS

Of the 1508 patients enrolled in the RENAL study, complete FB data to ICU discharge or 28 days or death (whichever occurred first) were available for 1453 (96.3%). During ICU stay, 705 (48.2%) patients had a positive MDFB and 748 (51.8%) a negative MDFB develop. The characteristics and outcomes of these patients are compared in Table 1. Patients with a negative MDFB had lower Acute Physiology and Chronic Health Evaluation III and cardiovascular SOFA scores at randomization and were less likely to have been admitted from the emergency department. Among patient with a negative MDFB, 241 (32.3%) had died by 90 days after randomization, compared with 403 (57.2%) in the positive MDFB group ($p < .0001$). Furthermore, survivors had a negative MDFB whereas nonsurvivors had a positive MDFB (Table 2).

The difference in MDFB between survivors and nonsurvivors was detectable on the day of randomization and persisted on subsequent days (Fig. 1). On day 1, both groups had a positive MDFB. However, survivors had a more negative MDFB, reached a near-neutral MDFB the next day (day 2), and had a negative MDFB every day thereafter. Nonsurvivors reached a slightly negative MDFB only by day 4, remained with a near-neutral MDFB for a few days, returned to a positive MDFB by day 9, and remained with a positive MDFB thereafter. Patients with organ edema, however, had a more negative MDFB (−26.3 vs. +230.8 mL; $p < .0001$) and cumulative FB (−1616 vs. 724.6 mL; $p < .0001$; see online Appendix for further details).

Patients with a negative MDFB had an average of 4.5 days of vasopressor therapy vs. 5.0 days for patients with a positive FB ($p = .07$). Patients who were receiving vasopressor therapy at randomization had more negative MDFB days than patients not receiving vasopressor support (5.5 vs. 4.8 days; $p = .01$) and, during treatment, there were more negative MDFB days when the cardiovascular SOFA score was 0-2 than when it was 3 or 4 (4.7 vs. 3.4

Table 2. Daily and cumulative fluid balance according to survival status at 90 days after randomization

Fluid Balance, No. of Patients, Mean, SD, Quartile 1 Median, Quartile 3 Days With Missing Data	Nonsurvivors	Survivors	p^a
Mean daily FB during time in ICU[a]	644 560.0 (1494) −274 305.2 1116 10	808 −234 (852) −738 −226 254.9 2	<.0001
Weight-adjusted mean daily FB during time in ICU	644 7.2 (19.1) −3.6, 4.0 14.3 10	808 −2.7 (10.8) −8.7 −2.6 3.1 2	<.0001
Mean cumulative FB during time in ICU	644 1755 (9061) −2310, 1518, 5922 10	808 −1941 (11,000) −6863, −1928, 2240 2	<.0001
Weight-adjusted mean cumulative FB during time in ICU	644 22.5 (119) −29.5, 18.8, 75.2 10	808 −22.3 (131) −85.0, −23.6, 28.4 2	<.0001

FB, fluid balance; ICU, intensive care unit.

[a]Refers to index admission to a maximum of 28 days.

Weight adjusted indicates FB in mL/patient weight in kg. Patient numbers add to 1452. Patient 1453 had missing outcome data.

days; $p < .0001$). In addition, in patients with an albumin level below the median at baseline, a negative MDFB was recorded on 5.4 days compared with 5.2 days in patients with an albumin level above the median ($p = .66$). Finally, a similar amount of albumin was administered to patients with a negative vs. positive MDFB (68.8 vs. 76.3 g; $p = .29$).

There was a more positive MDFB in patients with a renal SOFA score of 1 to 2 compared to patients with a score of 3 or 4 (Supplemental Digital Content 1, http://links.lww.com/CCM/A408). Finally, cessation of CRRT was associated with decreased ability to maintain a neutral MDFB. The MDFB was +20.9 mL/day during 4329 CRRT days but +402.2 mL ($p = .0035$) on the 1,150 days after CRRT was stopped (Supplemental Digital Content 1, (http://links.lww.com/CCM/A408).

On univariate analysis, all measures of FB considered and several baseline variables had a significant association with 90-day mortality (online Appendix). On multivariable logistic regression analysis, however, only a few of these variables remained independently associated with 90-day mortality (Table 3). Importantly, a negative MDFB was associated with a close to 70% reduction in the odds ratio for death at 90 days. Essentially identical findings were seen when the MDFB during study treatment was used in the model or when the model was applied to patients with significant organ edema (n = 639) or without clinically significant organ edema (n = 814) at randomization (online Appendix). These findings were not materially affected by the presence or absence of sepsis or by the inclusion of a propensity score (Supplemental Digital Content 1, http://links.lww.com/CCM/A408).

Survival plots were also compared according to the presence or absence of a positive MDFB in the first 2 days after randomization and from day 2 until the end of data collection during the index ICU admissions. Both analyses showed increased mortality in patients with early or late positive MDFB ($p < .0001$) (Figs. 2 and 3). These differences in outcome were confirmed by Cox proportional hazards modeling comparing quartiles of MDFB (Fig. 4). Assessment of quintiles of MDFB showed a progressive increase in mortality, with the greatest positive MDFB quintile having a five-fold increase in the risk of death compared to the first quintile (Fig. 5).

All measures of positive FB also showed an association with decreased RRT-free days at day 90 after randomization (online Appendix). On multivariable linear regression analysis, however, only a few of these variables remained independently associated with decreased RRT-free days at 90 days, including a positive MDFB ($p = .0017$). Similar findings were seen when the outcomes were mechanical ventilation-free days, ICU-free days, or hospital-free days (Supplemental Tables, Supplemental Digital Content 1, http://links.lww.com/CCM/A408).

When these associations was tested by means of additional univariate and sensitivity analyses, comparisons, time-dependent modeling, repeated measure modeling, and Cox proportional hazards modeling, the findings remained essentially unchanged (Supplemental Digital Content 1, http://links.lww.com/CCM/A408).

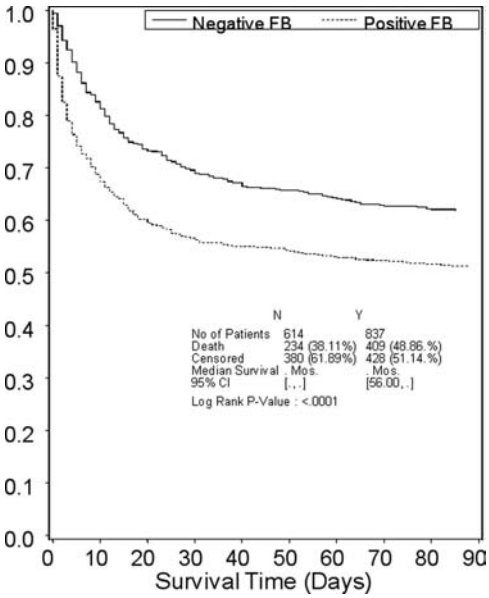

Figure 2. Kaplan Meier graph of survival plots from randomization to day 90 stratified by the presence or absence of a positive fluid balance (*FB*) from day 0 to day 2. The findings are similar to those seen when separating patients according to FB later during their time in intensive care unit. *CI*, confidence interval.

DISCUSSION

Statement of Key Findings

Using data from a large, multicenter RCT of the intensity of CRRT in critically ill patients with AKI, we assessed the association between FB from randomization until ICU discharge or 28 days or death (whichever occurred first) and outcome. We found that during the time of observation in ICU, a negative MDFB was associated with a significantly lower mortality than a positive MDFB and that whereas survivors had a negative MDFB, nonsurvivors had a positive MDFB. This key observation was true even when FB in the first 48 hrs only was considered. Furthermore, a negative MDFB was independently associated with a near 70% decrease in the odds ratio for mortality. This relationship was present in patients with or without the

Table 3. Multivariable logistic regression with death at 90 days after randomization as outcome[a]

Variable	Effect (Discrete Variable)	Odds Ratio	95% Confidence Interval	*p*
Negative mean daily fluid balance during index admission to intensive care unit[b]	No vs. yes	0.318	0.24-0.43	<.0001
Age		1.033	1.02-1.04	<.0001
Time from intensive care unit admission to randomization (d)		1.002	1.00-1.04	0.0065
Acute Physiology and Chronic Health Evaluation III score		1.012	1.01-1.02	0.0002
Sequential Organ Failure Assessment liver (score)		1.224	1.07-1.40	0.0033
International normalized ratio for prothrombin time		1.277	1.08-1.51	0.0047

[a]Only variables with $p < .05$ presented; [b]data collected to a maximum of 28 days.

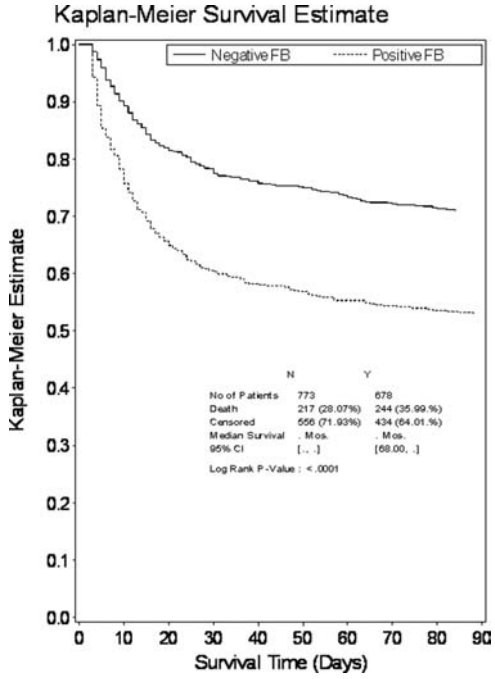

Figure 3. Kaplan Meier graph of survival time from randomization to day 90 stratified by the presence or absence of a positive fluid balance (*FB*) after the first 2 days of treatment had been removed and including all FB assessment over the index intensive care unit admission. The difference in outcome is similar in nature to that seen when separating patients according to FB in the first 2 days of management and is highly significant. *CI*, confidence interval.

clinical diagnosis of significant edema at randomization. A negative MDFB was also associated with better outcomes in terms of RRT-free days, mechanical ventilation-free days, ICU-free days, and hospital-free days. When we applied propensity analysis, time-dependent modeling, repeated measure modeling, and Cox proportional hazards modeling, our findings remained unchanged.

Comparison With Previous Studies

Our findings are in agreement with and expand those of previous observational studies (6–13). In all of these studies, the relationship between FB and outcome typically related to both before and during treatment with RRT. However, the relationship between timing of RRT and FB was not studied. In our patients, no numerical information was available to estimate the degree of fluid overload before RRT. However, 639 patients were assessed as having clinically significant vital organ edema at randomization. The cumulative FB difference between survivors and nonsurvivors was close to 5% of body weight (approximately 3.5 L in an average 80-kg person). This difference in cumulative FB has been previously associated with unfavorable outcome (10, 11).

Our data expand our understanding of the relationship between FB and outcome. They provide independently monitored and verified information with independent data verification and negligible missing data. They also provide such information in the setting of essentially exclusive CRRT use. This difference is important because intermittent hemodialysis may result in a more positive FB (11) and has limited ability to control volume status in patients with AKI (11). With CRRT, volume control is typically always possible. Thus, FB in this setting likely reflects therapeutic choices rather than technical limitations (22–24).

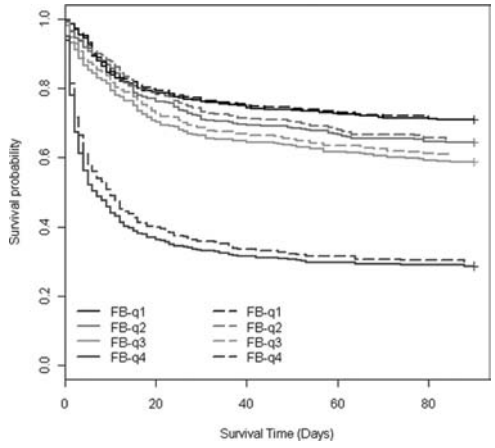

Figure 4. Cox proportional hazards survival plot with adjustment for treatment group, all Acute Physiology and Chronic Health Evaluation III diagnostic groups, daily use of continuous renal replacement therapy, age, time from intensive care unit to randomization, presence of sepsis, Sequential Organ Failure Assessment (SOFA) respiratory score, SOFA coagulation score, SOFA liver score, SOFA cardiovascular score, SOFA renal score, presence of nonrenal organ failure, international normalized ratio for prothrombin time, activate partial thromboplastin time, platelet count, serum creatinine, Pao_2/Fio_2 ratio, $Paco_2$ days, and clinical diagnosis of significant edema at randomization. The quartile 1 to quartile 4 refer to fluid balance (*FB*). The *broken line* refers to patients with a positive mean daily FB, whereas the *continuous line* refers to patients with a negative mean daily FB. In both groups of patients, there is a significant increase in mortality according to quartile of FB, such that the greater the mean daily FB, the greater the risk of death. *q*, quartile.

Significance of Study Findings

Our study provides additional evidence of an independent association between a negative FB and decreased 90-day mortality. It also raises the possibility that the pursuit of a positive FB is potentially deleterious.

The association between a positive FB and adverse outcome may simply represent the fact that a positive FB is a marker of illness severity, as suggested by higher Acute Physiology and Chronic Health Evaluation III and cardiovascular SOFA scores at randomization. However, the association remained after adjustment for propensity and all available markers of illness severity at randomization, suggesting that differences in illness severity may not fully account for our findings. The consistent association between a positive FB and unfavorable outcome suggests the need to exert prudence with fluid administration in patients with AKI (22). If a negative FB in considered unsafe because of patient instability, then our findings suggest the need to consider a negative FB as soon as it appears clinically safe to do so.

A positive FB may simultaneously act as a biomarker and mediator of illness

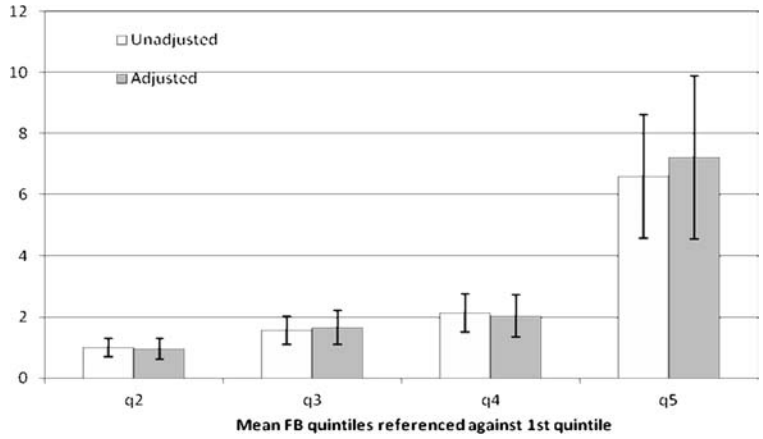

Figure 5. Changes in 90-day mortality according to quintiles of mean daily fluid balance (*FB*) during study observation period with or without adjustment for baseline characteristics.

severity, with each aspect occurring to a degree that cannot yet be quantified. Only RCTs can address these issues. However, such trials are only justified if observational studies such as ours support the need to test the hypothesis that the pursuit of a negative FB may improve outcomes. This hypothesis now seems to apply to FB management in AKI patients. This is similar to the field of acute lung injury, in which the hypothesis that a positive FB negatively impacts outcome was tested and confirmed true in RCT.

Study Strengths and Limitations

We cannot provide information on FB before treatment. However, although the definition of edema had a subjective component, close to 44% had edema at randomization, suggesting fluid overload. Their inclusion in multivariable analysis did not affect studies finding the association between a positive FB and outcome, and such patients behaved in relation to FB in the same way as those without edema at randomization. Despite such limitations, a relationship still emerged between FB and outcome, suggesting that FB may be an important physiologic variable and that its management may affect patient-centered outcomes. We reported the association of FB with a variety of intervention-free days-related outcomes. Such "intervention-free days" were chosen in preference to "duration of treatment days" because, although both outcome measures are confounded by the competing effect of mortality, free-days penalize mortality by allocating a value of 0 intervention free-days to patients who die while receiving treatment, whereas the "duration of treatment days" approach "rewards" mortality by allocating it a value of 0 treatment days.

Finally, as in all other observational studies, the relationship between FB and outcome may not be causal. We note, however, that our findings are analogous with an RCT in patients with acute lung injury (21) and observational studies in septic patients (25), and are suggestive of a functional relationship between an observed variable (FB in this case) and outcome (26). In addition, a possible causal relationship between a 2- and 3-kg fluid-induced gain in body weight (as seen in our patients) and outcome is supported by randomized controlled evidence (27) showing a progressive increase in complications (anastomotic breakdown, sepsis, bleeding, pulmonary edema, and arrhythmias), with increases from 0.5 to <2.5 to >2.5 kg in postoperative weight. Such complications appear biologically plausible because gut edema can weaken anastomotic strength (28) and function (29, 30), excessive fluid therapy can induce dilutional coagulopathy (31), pulmonary edema can cause hypoxemia, which, in turn, can predispose to arrhythmias, and cardiac edema can also contribute to such complications (29).

Table 4. Multivariable linear regression with renal replacement therapy-free days as outcome

Variable	Estimates	Standard Error	*p*
Intercept	−142.02968	80.90755	.0800
Positive mean daily fluid balance during index intensive care unit admission*	−4.29606	1.35909	.0017
Patients weight (kg)	0.07610	0.03859	.0493
Time from intensive care unit admission to randomization (days)	−0.01299	0.00485	.0077
Overall Sequential Organ Failure Assessment score (all nonmissing organ scores lumped together/5)	−3.68006	1.19039	.0021
Chloride (mmol/L)	0.35592	0.12614	.0050
pH	20.81819	10.26559	.0432

Only variables with $p < .05$ presented.

Future Investigations

Our study suggests that FB (a variable that can be manipulated during CRRT) may affect patient outcome in patients with AKI. Further investigations should now be directed at testing the feasibility of the conservative vs. liberal approaches of RCTs to FB in patients with or at high risk for AKI in a manner similar to studies conducted in patients with acute lung injury (21).

CONCLUSION

In the RENAL study, patients with a positive FB had higher mortality rate than those with a negative FB. After correction for multiple confounding variables and the application of different statistical modeling techniques, a negative FB was independently associated with a decreased risk of death at 90 days. These findings suggest the need for RCTs to test the hypothesis that a conservative FB can improve outcome in patients with AKI.

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APPENDIX

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Chapter 8

Early acid-base and blood pressure effects of continuous renal replacement therapy intensity in patients with metabolic acidosis

Early acid–base and blood pressure effects of continuous renal replacement therapy intensity in patients with metabolic acidosis

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ORIGINAL

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Abstract *Purpose:* In acute kidney injury patients, metabolic acidosis is common. Its severity, duration, and associated changes in mean arterial pressure (MAP) and vasopressor therapy may be affected by the intensity of continuous renal replacement therapy (CRRT). We aimed to compare key aspects of acidosis and MAP and vasopressor therapy in patients treated with two different CRRT intensities. *Methods:* We studied a nested cohort of 115 patients from two tertiary intensive care units (ICUs) within a large multicenter randomized controlled trial treated with lower intensity (LI) or higher intensity (HI) CRRT. *Results:* Levels of metabolic acidosis at randomization were similar [base excess (BE) of -8 ± 8 vs. -8 ± 7 mEq/l; $p = 0.76$]. Speed of BE correction did not differ between the two groups. However, the HI group had a greater increase in MAP from baseline to 24 h (7 ± 3 vs. 0 ± 3 mmHg; $p < 0.01$) and a greater decrease in norepinephrine dose (from 12.5 to 3.5 vs. 5 to 2.5 μg/min; $p < 0.05$). The correlation (r) coefficients between absolute change in MAP and norepinephrine (NE) dose versus change in BE were 0.05 and −0.37, respectively. *Conclusions:* Overall, LI and HI CRRT have similar acid–base effects in patients with acidosis. However, HI was associated with greater improvements in MAP and vasopressor requirements (clinical trial no. NCT00221013).

Keywords Acidosis · Acid–base · Acidemia · Norepinephrine · Alkalosis · Base excess · Bicarbonate · pH · Continuous renal replacement therapy · Hemodialysis · Strong ion difference

Introduction

Acid–base homeostasis is a key therapeutic target in critically ill patients [1, 2]. However, acidosis is common in the critically ill [3]. Such acidosis is an independent predictor of unfavorable outcome in this population [4, 5]. In patients with acute kidney injury (AKI), metabolic acidosis is especially common [6]. Although the exact

mechanisms of metabolic acidosis in AKI are complex, excess of retained metabolic acids is likely to contribute, together with other general acid–base disorders of critical illness (hyperlactatemia and/or hyperchloremia) [7, 8]. Depending on its severity, correction may require different levels of intervention including renal replacement therapy (RRT) [9].

Despite the logical expectation that RRT should improve metabolic acidosis, studies have reported that its effect on acid–base status is likely dependent on the nature of acidosis (anion gap positive vs. non-anion gap acidosis), its intensity, choice of buffer, ability of the body to metabolize buffer to bicarbonate, site of delivery of the buffer, and quantity of buffer delivered [10–12]. In addition, the plasma concentration of solutes available for ultrafiltration, and the rate of ultrafiltration also appear to determine the effect of RRT on acid–base status [13, 14]. In this regard, although under most circumstances other buffers are adequate, bicarbonate-based replacement or dialysis solutions more predictably and consistently reverse metabolic acidosis [11]. However, once bicarbonate is used as replacement fluid and dialysate fluid, little is known about the impact of CRRT intensity on the speed and extent of correction of metabolic acidosis in advanced AKI. In particular, it is unknown whether applying more intensive CRRT would lead to faster and/or greater resolution of acidosis in the early (first 24 h) treatment period. Also, given concerns that acidosis and/or acidemia might lower MAP and increase vasopressor requirements, it is unknown whether such correction would be accompanied by an effect on mean arterial pressure.

We hypothesized that, in the first 24 h, higher intensity (HI) CRRT would reverse metabolic acidosis at a faster rate and to a greater degree than lower intensity (LI) CRRT, and thus had correction of acidosis in the first 24 h as our primary endpoint. We also hypothesized that such changes would be accompanied by a greater increase in MAP, and therefore had improved MAP at 24 h as our secondary endpoint. We tested these hypotheses by conducting a nested cohort study within the randomized evaluation of normal versus augmented level (RENAL) Replacement Therapy Study, a multicenter randomized controlled study comparing two levels of CRRT intensity [15].

Methods

The study involved a nested cohort of patients from two centers within the RENAL study in whom detailed data on acid–base status were obtained during the first 24 h of CRRT treatment. The RENAL study was a multicenter, prospective, randomized trial of two levels of intensity of continuous renal replacement therapy (CRRT) originally in 1,508 critically ill patients with acute kidney injury conducted in 35 ICUs in Australia and New Zealand [15]. The study was approved by the Human Research Ethics Committees of the University of Sydney and all participating institutions.

The methodological details of the RENAL study were recently reported [15]. In brief, patients were eligible for enrollment if they were critically ill adults who had AKI, were deemed to require RRT by the treating clinician, and fulfilled predefined criteria [15]. Eligible patients were randomly assigned to continuous venovenous hemodiafiltration (CVVHDF) with effluent flow at 25 ml/kg/h (lower intensity, LI) or 40 ml/kg/h (higher intensity, HI). 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. Blood flow was kept above 150 ml/min. Fluid was removed by decreasing the flow of the replacement fluid and of the dialysate in equal proportion, so that effluent exceeded them 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. Hemosol contains sodium ion (Na^+, 140 mmol/l), chloride ion (Cl^-, 109.5 mmol/l), bicarbonate (HCO_3^-, 32 mmol/l), lactate (3 mmol/l), calcium ion (Ca^{2+}, 1.75 mmol/l), and magnesium ion (Mg^{2+}, 0.5 mmol/l).

All patients were anticoagulated with unfractionated heparin with target at the attending clinician's discretion.

The intensive care management of the patients including CO_2 tension in arterial blood ($PaCO_2$) and MAP aims were set by the treating physicians. Study treatment was discontinued on death, discharge from ICU, or recovery of renal function.

Measurements

In all patients arterial blood pH, plasma lactate, $PaCO_2$, K, Na, Mg, ionized Ca (iCa), Cl, phosphate (Phos), albumin (alb), creatinine, and urea levels, MAP, and dose of norepinephrine in μg/min were recorded 2-hourly for 24 h.

Calculations

Plasma standard HCO_3^- levels and BE values were calculated by blood gas machines.

The strong ion gap (SIG) [16] was calculated as the difference between the apparent (SIDa) and effective (SIDe) strong ion difference [17, 18], where

$$\mathrm{SIDa} = [\mathrm{Na}^+] + [\mathrm{K}^+] + 2 \times [\mathrm{iCa}^{2+}] + 2 \times [\mathrm{Mg}^{2+}] - [\mathrm{Cl}^-] - [\text{L-lactate}]$$

and [16]

$$\mathrm{SIDe} = 1000 \times 2.46 \times 10^{-11} \times \mathrm{PaCO_2}/10^{-\mathrm{pH}} + \mathrm{Alb} \times (0.123 \times \mathrm{pH} - 0.631) + \mathrm{Phos} \times (0.309 \times \mathrm{pH} - 0.469)\,.$$

Statistical analysis

Data are expressed as mean with standard deviation (SD) for normally distributed variables and as median and interquartile range (IQR) for non-normally distributed variables.

To adjust for the effect of any missing data, calculations were made with and without imputations for missing data. Imputations were done by calculating the mean of the value immediately before and after the missing value. If a value was missing at the end of the observational period, the "last value carry forward" method was used. The calculations with the two datasets corresponded well to one another, thus only analysis based on original data without imputations is reported, unless otherwise stated.

Comparisons were made using the *z*-test for dichotomous variables, *t* test or analysis of variance (ANOVA) as appropriate for repeated measurements for variables with normal distribution and the Mann–Whitney test or Wilcoxon matched-pairs test for variables with non-normal distribution. Spearman's rank test was used for calculating correlation coefficients. $p < 0.05$ was considered significant. Statistical analyses were performed by STATISTICA™ software, version 10 (StatSoft, Tulsa, OK, USA).

Results

Patient characteristics

We studied 115 patients, of whom 59 (51 %) were randomized into the lower intensity (LI) group and 56 (49 %) into the higher intensity (HI) group. The two groups were comparable in terms of age, mortality, severity of illness and organ failure, and delivered CRRT time (Table 1). All but one patient had an abnormal anion gap, and 28 of the 115 patients (24 %) had plasma lactate over 4 mmol/l. Discharge diagnosis groups are provided in Table 2.

At 28 days, 45 (39 %) patients were dead: 24 (41 %) in the LI group and 21 (38 %) in the HI group. The most common ICU admission diagnosis was sepsis with AKI ($n = 43$, 37 % of total), followed by postoperative AKI ($n = 21$, 18 % of total), AKI due to primary renal disease ($n = 19$, 17 % of total), and AKI secondary to other medical conditions ($n = 32$, 28 % of total).

Acid–base effects

Biochemical, acid–base, and MAP values at baseline and 24 h are given in Table 3. Overall, acidosis improved similarly in both groups. In particular, BE increased similarly from 0 to 24 h in both groups (Fig. 1).

Normal BE between −2 to +2 mmol/l at 24 h was achieved in 29 (49 %) LI patients and 29 (52 %) HI patients.

Table 2 ICU discharge diagnosis groups for cohort ($n = 115$)

	n	Percentage of total
Medical diagnoses	89	77
Infectious conditions	34	30
Cardiac conditions	6	5
Respiratory conditions	2	2
Genitourinary conditions	25	22
Hepatic conditions	8	7
Other medical conditions	14	12
Surgical diagnoses	26	23
General surgical conditions	13	11
Cardiac surgical conditions	9	8
Vascular surgical conditions	3	3
Trauma	1	1

Table 1 Characteristics of the study population according to treatment allocation

	Overall population	LI group	HI group	*p*-Value
Sex (% male)	83/115 (72 %)	41/59 (70 %)	42/56 (75 %)	0.51
Day 28 mortality (% dead)	45/115 (39 %)	24/59 (41 %)	21/56 (38 %)	0.70
Age (IQR), years	67 (19)	66 (18)	69 (19)	0.24
APACHE III (IQR)	103 (30)	100 (35)	107 (33)	0.09
SOFA (IQR)	11 (6)	11 (6)	11 (6)	0.43
Hours on CRRT (IQR)	21 (6)	21 (7)	22 (6)	0.46

p-Values refer to intergroup differences

LI lower intensity, *HI* high intensity, *APACHE* Acute Physiology and Chronic Health Evaluation score, *CRRT* continuous renal replacement therapy, *SOFA* Sequential Organ Failure Assessment score

Table 3 Change in biochemical and physiologic data in the two study groups from baseline to 24 h

Change from baseline to 24 h of CRRT	Lower intensity CRRT			Higher intensity CRRT		
	0	24	*p*-Value	0	24	*p*-Value
pH	7.30 ± 0.12	7.36 ± 0.12	<0.001	7.29 ± 0.11	7.38 ± 0.07	<0.001
HCO_3^- (mmol/l)	18 ± 6	22 ± 4	<0.001	18 ± 6	23 ± 6	<0.001
BE (mEq/l)	−8 ± 8	−3 ± 6	<0.001	−8 ± 7	−2 ± 4	<0.001
SIDa (mmol/l)	38 ± 6	38 ± 5	0.38	38 ± 6	37 ± 4	0.17
SIG (mmol/l)	10 ± 4	8 ± 14	0.30	10 ± 5	5 ± 4	<0.001
Lactate (mmol/l)	2.4 (1.3–4.6)	1.8 (1.4–2.9)	0.83	2.2 (1.6–3.8)	1.4 (1.1–2.5)	<0.01
Chloride (mmol/l)	104 ± 7	103 ± 4	0.24	103 ± 8	103 ± 3	0.97
MAP (mmHg)	78 ± 11	78 ± 12	0.93	73 ± 11	81 ± 15	<0.001
Norepinephrine dose (μg/min)	5 (0–14)	3 (0–11)	0.53	13 (0–22)	4 (0–14)	<0.001

Values are given at 0 h (at the start of CRRT) and at 24 h of CRRT
Data are given as mean ± standard deviation or median (interquartile range)
p-Values refer to intragroup difference from 0 to 24 h

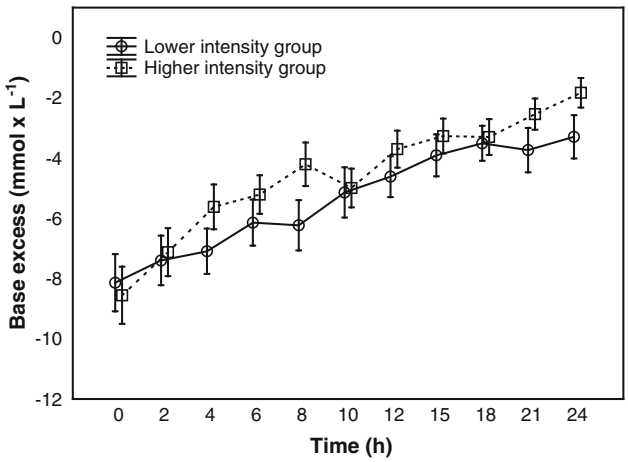

Fig. 1 Changes in base excess (BE) levels in the first 24 h of treatment in patients receiving lower intensity and higher intensity CRRT (mean ± standard error, SE)

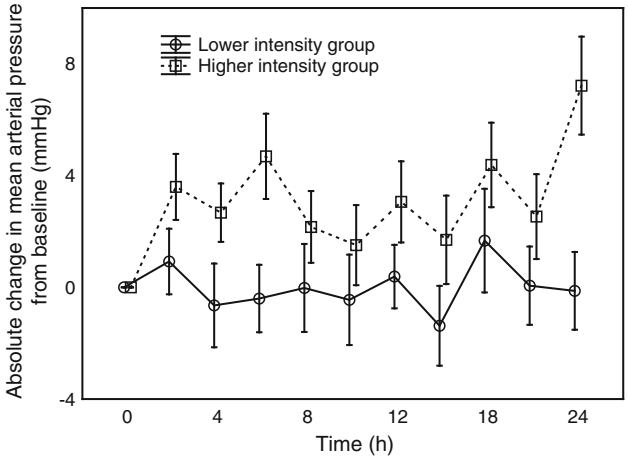

Fig. 2 Absolute changes in mean arterial pressure (MAP) from baseline in the first 24 h of treatment in patients receiving lower intensity and higher intensity CRRT (mean ± SE)

Effect on mean arterial pressure and norepinephrine dose

MAP was higher in the LI group at baseline compared with the HI group (78 ± 12 vs. 73 ± 11 mmHg; $p < 0.05$) in the overall population. However, the absolute change in MAP from baseline to 24 h was greater in the HI group ($p < 0.001$) (Fig. 2). The absolute change in MAP did not correlate with the absolute change in BE ($r = 0.05$).

The dose of norepinephrine differed between the groups at baseline ($p < 0.05$; Table 3). The absolute change in norepinephrine dose from baseline to 24 h (Fig. 3) was greater in the HI group (−7 ± 5 vs. 0 ± 5 μg/min; $p < 0.05$) than in the LI group. This difference in dose remained significant even when patients without baseline norepinephrine treatment were excluded (25 out of 59 patients in the LI group and 15 out of 52 patients in the HI group). The correlation between

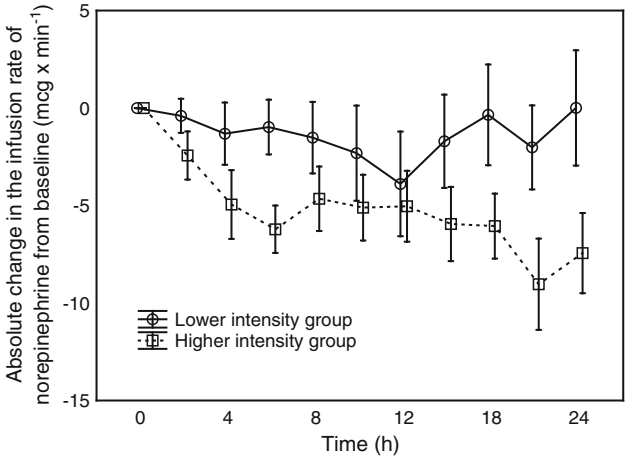

Fig. 3 Absolute changes in the infusion rate of norepinephrine from baseline in the first 24 h of treatment in patients receiving lower intensity and higher intensity CRRT (mean ± SE)

absolute change in norepinephrine dose and the absolute change in BE was weak ($r = -0.37$).

Discussion

Key findings

We conducted a nested cohort study within the RENAL trial to test whether HI CRRT would result in faster and/or greater early correction of acidosis and whether it would also affect MAP and NE treatment. Overall, we found that HI CRRT achieved a similar rate and magnitude of acidosis correction compared with LI CRRT. However, HI CRRT resulted in a greater increase in blood pressure and a greater decrease in norepinephrine requirements. These changes did not correlate with changes in pH or BE.

Relationship to previous studies

The effect of CRRT on acid–base balance appears determined by the plasma concentration of solutes available for ultrafiltration, the composition of the dialysis or replacement fluid, the intensity of ultrafiltration, and body weight [13, 14]. Our study showed, as expected, that bicarbonate-based CRRT attenuates metabolic acidosis [10–12]. Although the effects of bicarbonate-based CRRT on acid–base disorders have been investigated previously [19], our study is the largest study of the acid–base effect of CRRT intensity within a randomized trial.

The overall reversal of acidosis was similar in the LI and HI groups in terms of pH change and change in HCO_3^- levels and BE.

Despite the similar effects on BE, HI and LI had a different effect on SIG, which decreased more in the HI group. This effect could be consistent with the view that the removal of unmeasured organic anions by CRRT is increased with greater intensity [7, 20]. However, since SIG decreased similarly in both HI and LI groups in the severe acidosis subgroup, this effect may not entirely be related to CRRT intensity or only operate at less severe acid–base disturbances. In contrast, there were no or minimal effects of CRRT on the SID, a major determinant of acid–base status [16]. However, one ion (potassium) was affected by CRRT intensity. Such decrease in plasma potassium levels appears due to direct clearance by CRRT rather than a pH effect [21].

CRRT has been previously associated with improved MAP in animal models of sepsis and in humans [22–25]. However, no controlled studies have compared two intensities of CRRT in terms of their effect on MAP and vasopressor requirements [26]. We found that MAP increased and vasopressor requirements decreased with HI CRRT. Although decreased norepinephrine requirements could be attributed to normalization of pH, this was not different between the two groups and cannot be logically used to explain our findings [27, 28]. Cooling by CRRT at higher intensity may also explain changes in MAP. However, in all cases fluids were warmed to 37 °C or more, making this mechanism somewhat unlikely. A potential alternative mechanism could be more efficient removal of biologic mediators responsible for hypotension and/or vasodilatation [23, 29–31]. Some of these mediators may have contributed to the changes in SIG as well as inducing hypotension. Our study, however, cannot provide a mechanistic analysis of the physiological effects observed.

Implications

Our study suggests that acidemia is generally effectively reversed during CRRT after 24 h of therapy. This information could be of interest to clinicians wishing to correct metabolic acidosis in patients with severe AKI, but it is not clear if it would actually change the management of these patients. Additionally, the findings that higher intensity CRRT improves MAP and reduces vasopressor doses may assist clinicians dealing with patients with the combination of acidosis, severe hypotension, and vasopressor requirements during early CRRT. Although bicarbonate buffer was used in this study, other buffers may have similar effects on acid–base balance.

Strengths and limitations

This study is the largest investigating the effect of CRRT dialysate and replacement fluid flow on acid–base status within a randomized controlled trial (RCT); data collection was extensive, numerical, and based on blood gas machine output or independently recorded by the bedside nurse. These aspects of the study make bias unlikely. As this is a nested cohort study of the RENAL trial, thus a substudy, selection bias introduced by studying a subpopulation can influence results. However, patients included in this study were recruited by including all patients from two centers of the RENAL study, their age and illness severity are similar to those reported for the whole population of RENAL trial patients [15], and the cohort represents a mixture of patients typically seen in general intensive care units. Others have reported that nested cohort studies have a design that preserves the validity of the original population when selection bias can be avoided [32].

Another consequence of our methodology is that our patients were not recruited and randomized to test the specific hypothesis of this study. However, since a majority of study patients had metabolic acidosis, this population was particularly useful to investigate the acid–base effects of CRRT in this setting. This study investigated a specific CRRT setup (bicarbonate-based continuous venovenous hemodiafiltration, with fixed blood flow and

postfilter replacement); conclusions from this study, therefore, may not apply to other CRRT techniques.

Finally, our study was only conducted for 24 h, thus we cannot comment on the later effects associated with CRRT [33]. However, most acid–base disturbances are reversed within this time period, and if CRRT fails to restore acid–base homeostasis by 24 h, clinicians may choose additional therapies [34].

Future research

Further studies of CRRT intensity with other buffers (e.g., citrate) may be of interest given the evolution of therapy toward greater use of citrate as anticoagulant [35]. In addition, investigation of the mechanism by which HI CRRT improves MAP might provide insights into future therapeutic interventions.

Conclusions

In this nested cohort study within a large RCT, HI CRRT did not affect acid–base differently from LI CRRT overall. In addition, HI CRRT increased MAP and decreased norepinephrine requirements compared with LI CRRT. These physiological observations may be helpful to clinicians faced with the treatment of patients with combined AKI, metabolic acidosis, hypotension, and vasopressor therapy.

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Conflicts of interest Professor Cass was supported by a NHMRC Senior Research Fellowship. Professor Bellomo has received consulting fees from Gambro Pty Ltd. Professor Simon Finfer has received travel support to present research results at scientific meetings from Eli Lilly, Cardinal Health, and CSL Bioplasma. The George Institute for International Health, an independent not-for-profit institute affiliated with the University of Sydney, has received reimbursement for Professor Finfer's time as a steering committee member for studies sponsored by Eli Lilly and Eisai. The George Institute has received research funding from Servier, Novartis, Eisai, Merck, Sharp & Dohme, Pfizer Australia, Fresenius Kabi Deutschland GmbH, and Sanofi Aventis.

Appendix

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Chapter 9

The relationship between hypophosphataemia and outcomes during low-intensity and high intensity continuous renal replacement therapy

The relationship between hypophosphataemia and outcomes during low-intensity and high-intensity continuous renal replacement therapy

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ABSTRACT

Aim: To identify risk factors for development of hypophosphataemia in patients treated with two different intensities of continuous renal replacement therapy (CRRT) and to assess the independent association of hypophosphataemia with major clinical outcomes.

Materials and methods: We performed secondary analysis of data collected from 1441 patients during a large, multicentre randomised controlled trial of CRRT intensity. We allocated patients to two different intensities of CRRT (25 mL/kg/hour vs 40 mL/kg/hour of effluent generation) and obtained daily measurement of serum phosphate levels.

Results: We obtained 14 115 phosphate measurements and identified 462 patients (32.1%) with hypophosphataemia, with peak incidence on Day 2 and Day 3. With lower intensity CRRT, there were 58 episodes of hypophosphataemia/1000 patient days, compared with 112 episodes/1000 patient days with higher intensity CRRT ($P < 0.001$). On multivariable logistic regression analysis, higher intensity CRRT, female sex, higher Acute Physiology and Chronic Health Evaluation score and hypokalaemia were independently associated with an increased odds ratio (OR) for hypophosphataemia. On multivariable models, hypophosphataemia was associated with better clinical outcomes, but when analysis was confined to patients alive at 96 hours, hypophosphataemia was not independently associated with clinical outcomes.

Conclusions: Hypophosphataemia is common during CRRT and its incidence increases with greater CRRT intensity. Hypophosphataemia is not a robust independent predictor of mortality. Its greater incidence in the higher intensity CRRT arm of the Randomised Evaluation of Normal vs Augmented Level trial does not explain the lack of improved outcomes with such treatment.

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Phosphate is an essential part of structural cell membrane molecules (eg, phospholipids), energy sources (eg, adenosine triphosphate) and second messengers (eg, adenosine monophosphate).[1] These control mechanisms are disrupted by critical illness[2] and acute kidney injury (AKI) in particular.

When continuous renal replacement therapy (CRRT) is used in the treatment of severe AKI,[3,4] hypophosphataemia may develop, secondary to excess phosphate removal.[5,6] Hypophosphataemia has been associated in some studies with diaphragmatic weakness, increased risk of failed phosphate weaning and decreased myocardial contractility.[7-9] However, these studies did not take into account situations in which phosphate is concomitantly lowered by CRRT rather than by disease alone. As hypophosphataemia during CRRT may develop slowly and phosphate levels are likely to be regularly monitored, the clinical risk may be lower. In this setting, there is limited information on the timing, severity, duration and independent associations of hypophosphataemia with outcome. Such knowledge is important because of the reported greater incidence of hypophosphataemia during higher intensity CRRT in recent dialysis trials.[10,11] If hypophosphataemia independently contributes to a greater risk of mortality or morbidity, its more common occurrence with higher intensity CRRT might, at least partly, explain why such treatment fails to achieve a survival advantage.

The Randomised Evaluation of Normal vs Augmented Level (RENAL) study[12-15] is the largest randomised study of CRRT in patients with AKI to date. Because of its size, the availability of daily serum phosphate measurements and the two levels of CRRT intensity, we used RENAL trial data to explore the timing, severity, duration and predictors of hypophosphataemia during CRRT, and the possible independent association of hypophosphataemia with major clinical outcomes. In particular, we aimed to test the hypothesis that hypophosphataemia is independently associated with an increased risk of death in patients receiving CRRT.

Methods

The RENAL study was a multicentre, prospective, randomised trial of two levels of intensity of CRRT in 1508 critically ill patients with AKI, conducted in 35 intensive care units in Australia and New Zealand. The human research ethics committees of the University of Sydney and all participating institutions approved the study.

The methodological details of the RENAL study were recently reported.[12-15] In brief, patients were eligible for enrolment if they were critically ill adults who had AKI, were deemed to require CRRT by the treating clinician and fulfilled other predefined criteria. Eligible patients were randomly assigned to continuous venovenous haemodiafiltration with effluent flow at 40 mL/kg/hour (high intensity) or 25 mL/kg/hour (low intensity). Study treatment was discontinued on death, discharge from the ICU or recovery of renal function to dialysis independence. The primary study end point was death from any cause by Day 90.

Serum phosphate measurement and definitions

In all patients, daily phosphate measurements were performed and recorded every morning until the first occurrence of either death, ICU discharge or completion of 28 days from study randomisation (study treatment period).

For the purpose of this study, and in keeping with local normal reference values, hypophosphataemia was considered present when the serum phosphate level was < 0.6 mmol/L, a stricter definition than was originally applied in the RENAL study.[10] Hypophosphataemia was defined as mild if the serum phosphate level was between 0.4 mmol/L and 0.6 mmol/L, moderate if the serum phosphate level was between 0.2 mmol/L and 0.4 mmol/L, and severe if the serum phosphate level was below 0.2 mmol/L.

Persistent hypophosphataemia was defined by the presence of two serum phosphate levels in the hypophosphataemic range on two consecutive days, and recurrent hypophosphataemia was defined by the presence of two serum phosphate levels in the hypophosphataemic range on two non-consecutive days.

Statistical analysis

Continuous variables were expressed as means with SD for normally distributed variables, and as medians with interquartile ranges for non-normally distributed variables. Comparisons were made using the student *t* test or the Mann–Whitney test, where appropriate. Categorical variables were expressed as proportions and compared using the χ^2 test or the Fisher exact test, as appropriate.

Daily hypophosphataemia-related variables and all baseline variables (biochemical, demographic, clinical and illness severity-related variables) available at randomisation were used to create multivariable models, using survival to 90 days as the primary dependent outcome variable. Multivariable linear regression analysis was used to assess the possible independent relationship between hypophosphataemia and the following dependent variables: mechanical ventilation (MV)-free days, CRRT-free days and ICU-free days at 90-day follow-up. The unadjusted analysis of time to death within 90 days of randomisation is shown as Kaplan–Meier product limit estimates, and survival curves are compared using the log-rank test.

To test whether there was an independent association between mortality and hypophosphataemia, we sought to remove the competing and confounding effect of survival time on the probability of experiencing hypophosphataemia, death or other adverse outcomes. This is because hypophosphataemia was much more common from Day 0 to Day 4 and was still quite common from Day 4 to Day 7. Patients who died before Day 4 or Day 7 had a decreased chance of experiencing hypophosphataemia and hence created an artificial association between hypophosphataemia and decreased risk of death. To correct for this time-related bias, we repeated multivariable analysis for key clinical outcomes after excluding patients who had died before 96 hours and before Day 7.

For an additional sensitivity analysis, we applied competing risk analysis[16] and joint model analysis.[17] For the purpose of joint model development, we first completed two submodels: a longitudinal model of phosphate, taking into account treatment, age, sex and weight, and assuming an interaction between treatment and day after randomisation. Second, we developed a survival Cox model adjusted for treatment and Acute Physiology and Chronic Health Evaluation (APACHE) III score. We also performed Cox proportional hazards modelling for all major outcomes, and pattern analysis to detect whether pattern mixture modelling could be applied. Pattern mixture is an alternative approach for correction for informative dropout.[18] The pattern mixture models allow investigators to relax the assumptions that missing data are missing at random, by permitting group comparisons on available data within subgroups of patients who drop out early.

To adjust for multiple analysis, a two-sided value of $P < 0.01$ was taken to indicate statistical significance. Statistical analyses were performed and independently checked using SAS version 9.1 and R version 2.15.3.

Results

Of the 1508 patients enrolled in the RENAL study, complete daily serum phosphate data were available for 1441 patients (95.6%), for a total of 14 115 phosphate measurements, with survival follow-up available for 1440 patients.

Table 1. Baseline characteristics and outcomes of patients with at least one episode of hypophosphataemia*

Baseline characteristics	Patients without hypophosphataemia	Patients with hypophosphataemia	*P*
Sex	*N* = 979	*N* = 462	
Female, *n* (%)	316 (32.3%)	194 (42%)	0.0003
Male, *n* (%)	663 (67.7%)	268 (58%)	NA
Mechanical ventilation	*N* = 978	*N* = 462	
No, *n* (%)	281 (28.7%)	97 (21%)	0.0018
Yes, *n* (%)	697 (71.3%)	365 (79%)	NA
Non-operative admission diagnosis	*N* = 695	*N* = 334	
Cardiovascular, *n* (%)	340 (48.9%)	184 (55.1%)	0.0026
Genitourinary, *n* (%)	171 (24.6%)	56 (16.8%)	NA
Gastrointestinal, *n* (%)	52 (7.5%)	23 (6.9%)	NA
Haematological, *n* (%)	20 (2.9%)	1 (0.3%)	NA
Metabolic or endocrine, *n* (%)	11 (1.6%)	14 (4.2%)	NA
Neurological, *n* (%)	7 (1%)	4 (1.2%)	NA
Respiratory, *n* (%)	89 (12.8%)	50 (15%)	NA
Transplant, *n* (%)	3 (0.4%)	2 (0.6%)	NA
Severe sepsis at baseline	*N* = 978	*N* = 462	
No, *n* (%)	528 (54%)	204 (44.2%)	0.0005
Yes, *n* (%)	450 (46%)	258 (55.8%)	NA
Mean APACHE III score (SD)	100.8 (25.3), *N* = 977	105.2 (26.2), *N* = 461	0.0029
SOFA respiration category	*N* = 945	*N* = 452	
Normal, *n* (%)	60 (6.3%)	10 (2.2%)	0.0004
Dysfunction, *n* (%)	211 (22.3%)	83 (18.4%)	NA
Failure, *n* (%)	674 (71.3%)	359 (79.4%)	NA
Mean SOFA respiration score (SD)	2.7 (1), *N* = 945	2.9 (0.8), *N* = 452	< 0.0001
SOFA cardiovascular category	*N* = 977	*N* = 460	
Normal, *n* (%)	170 (17.4%)	51 (11.1%)	< 0.0001
Dysfunction, *n* (%)	141 (14.4%)	40 (8.7%)	NA
Failure, *n* (%)	666 (68.2%)	369 (80.2%)	NA
Mean SOFA cardiovascular score (SD)	2.7 (1.6), *N* = 977	3.1 (1.4), *N* = 460	< 0.0001
⩾ 1 non-renal organ failure (SOFA score 3–4)	*N* = 979	*N* = 461	
No, *n* (%)	146 (14.9%)	38 (8.2%)	0.0004
Yes, *n* (%)	833 (85.1%)	423 (91.8%)	NA
Mean potassium (mmol/L) (SD)	4.9 (0.9), *N* = 968	4.6 (0.9), *N* = 462	< 0.0001
Mean urea (mmol/L) (SD)	24.3 (12.7), *N* = 974	21.2 (12.1), *N* = 460	< 0.0001
Mean creatinine, μmol/L (SD)	350.7 (217), *N* = 974	307.2 (187), *N* = 462	0.0002
Mean phosphate, mmol/L (SD)	2.1 (0.8), *N* = 916	1.9 (0.8), *N* = 434	< 0.0001

NA = not applicable. APACHE = Acute Physiology and Chronic Health Evaluation. SOFA = sequential organ failure assessment. * Only significant variables shown.

During treatment, 462 patients (32.1%) developed at least one episode of hypophosphataemia, with an incidence of 58 episodes/1000 patient-days during low-intensity CRRT, compared with 112 episodes/1000 patient-days during high-intensity CRRT ($P < 0.001$). The characteristics of patients who developed at least one episode of hypophosphataemia are compared with those of patients without any episode of hypophosphataemia in Table 1. Patients who experienced hypophosphataemia were more likely to be female and have sepsis and a greater illness severity on admission and more likely to have a lower baseline phosphate level.

Among patients with at least one episode of hypophosphataemia, 158 of 461 (34.3%) had died at 90 days after randomisation, compared with 473 of 979 patients (48.3%) who had never experienced hypophosphataemia ($P < 0.0001$). Survivors were also more likely to have experienced hypophosphataemia overall and mild, moderate, severe, persistent or recurrent hypophosphataemia, than non-survivors (Table 2).

Mean daily phosphate levels, by treatment allocation, are shown in Figure 1, and show a similar pattern of early decrease in phosphate levels and recovery with consistently higher levels during low-intensity CRRT. Figure 2 shows that phosphate levels had similar time-related changes among surviving and non-surviving patients. However, in the first few days, levels were lower among surviving patients. Figure 3 shows the incidence of hypophosphataemia on each day after randomisation, by treatment allocation. The peak incidence of hypophosphataemia was on Day 3 and Day 4 after randomisation.

On multivariable analysis, CRRT intensity, female sex, APACHE III score and hypokalaemia were independent predictors of a greater risk of developing hypophosphataemia, while female sex and calorie intake predicted development to persistent hypophosphataemia (see Appendix 2, Table 2a and Appendix 2, Table 2b at http://www.cicm.org.au/journal.php).

Association with outcome

On multivariable logistic regression analysis, the occurrence of at least one episode of hypophosphataemia during study treatment was independently associated with a significantly *decreased* risk of 90-day mortality (see

Figure 1. Changes in mean serum phosphate levels, by treatment intensity

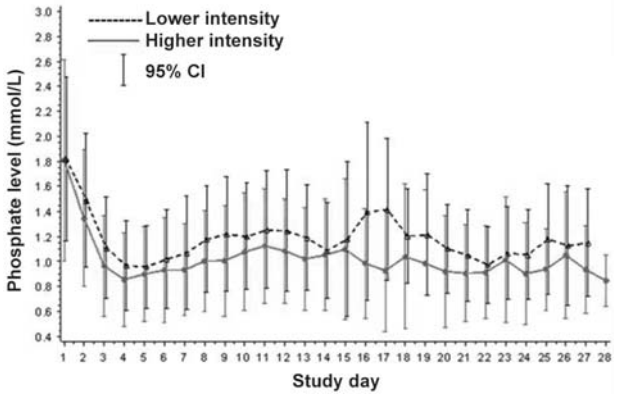


Figure 2. Changes in mean daily serum phosphate levels among survivors and non-survivors

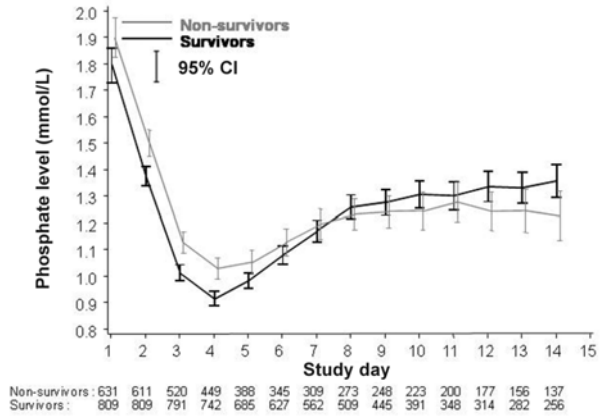


Figure 3. Timing and frequency of the occurrence of hypophosphataemia, by treatment intensity

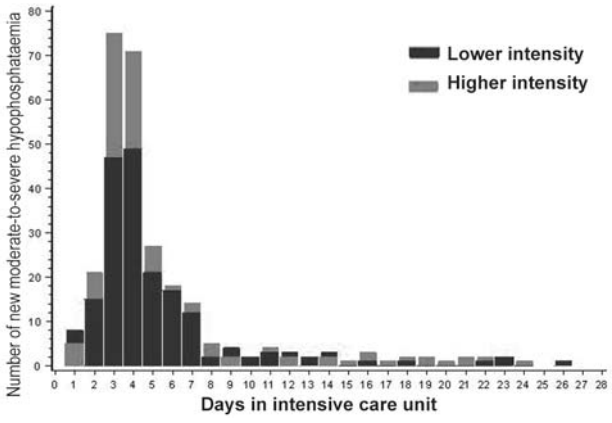


Table 2. Comparison of incidence, severity and persistence of episodes of hypophosphataemia among surviving and non-surviving patients

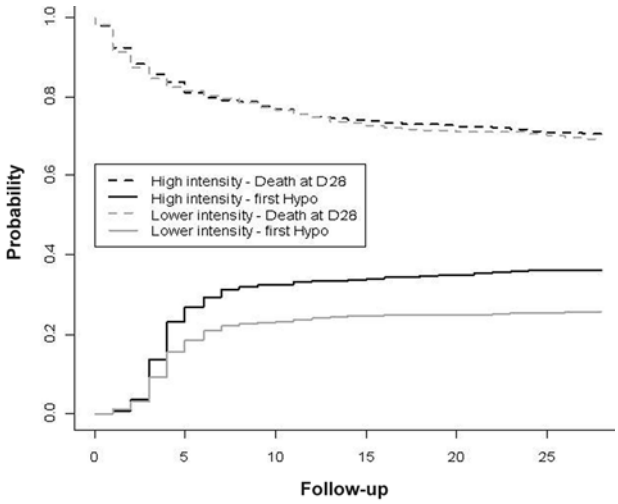
Baseline characteristic	Survivors (*N* = 809)	Non-survivors (*N* = 631)	*P*
⩾ 1 episode of hypophosphataemia, *n* (%)			
No	506 (62.5%)	473 (75%)	< 0.0001
Yes	303 (37.5%)	158 (25%)	
Severity of hypophosphataemia, *n* (%)			
No hypophosphataemia	506 (62.5%)	473 (75%)	< 0.0001
Mild	198 (24.5%)	119 (18.9%)	
Moderate	94 (11.6%)	35 (5.5%)	
Severe	11 (1.4%)	4 (0.6%)	
⩾ 1 episode of persistent hypophosphataemia, *n* (%)			
No	690 (85.3%)	568 (90.0%)	0.0074
Yes	119 (14.7%)	63 (10.0%)	
⩾ 1 episode of recurrent hypophosphataemia, *n* (%)			
No	628 (77.6%)	550 (87.2%)	< 0.0001
Yes	181 (22.4%)	81 (12.8%)	

Appendix 3, Table 3a at http://www.cicm.org.au/journal.php). This finding was not confirmed once the 1183 patients still alive after 96 hours and the 782 patients still alive after 7 days were assessed (see Appendix 3, Table 3b and Appendix 3, Table 3c at http://www.cicm.org.au/journal.php).

Cox proportional hazards modelling confirmed this pattern (see Appendix 4 at http://www.cicm.org.au/journal.php). Similar findings were seen when applying log-rank tests to survival time with Kaplan–Meier plots showing increased time to death with hypophosphataemia. This was corrected once analysis only was applied to patients who survived the first 96 hours (see Appendix 5 at http://www.cicm.org.au/journal.php).

On multivariable linear regression analysis, hypophosphataemia was associated with increased CRRT-free days, MV-free days, ICU-free days and hospital-free days after randomisation until Day 90. These findings were not confirmed once analysis was applied to patients who survived to 96 hours. Competing-risk analysis confirmed that the time to

Figure 4. Cumulative incidence function of the competing events of first hypophosphataemic episode and mortality*



* Shows a significant difference (the Gray test, $P < 0.0001$) in the incidence of hypophosphataemia induced by higher-intensity continuous renal replacement therapy. In both groups, essentially all episodes of hypophosphataemia have occurred by Day 7.

hypophosphataemia was shorter with high-intensity CRRT even when the competing risk of mortality was taken into account (Figure 4). The joint-model analysis also found no relationship between hypophosphataemia and outcome.

Discussion

Key findings

Using data from a large, multicentre, randomised controlled trial of the intensity of CRRT in critically ill patients with AKI, we assessed the incidence, timing and duration of hypophosphataemia and its association with major outcomes. We found that patients with hypophosphataemia had significantly decreased unadjusted mortality compared with patients who did not experience hypophosphataemia, and that surviving patients had a higher incidence of hypophosphataemia than non-surviving patients. Furthermore, when we estimated the independent association between hypophosphataemia and outcome at Day 90, we found that hypophosphataemia was independently associated with a decreased risk of death and with other improvements in patient-centered outcome such as CRRT-free days, MV-free days, ICU-free days and hospital-free days. However, these associations were confounded by the competing effect of mortality because the incidence of hypophosphataemia peaked at Day 4, and patients who died early were therefore less likely to experience such hypophosphataemia. Once we tested the robustness of the findings by adjusting for the biasing effect of survival time on the chance of developing hypophosphataemia, they could not be confirmed.

Comparison with previous studies

The association between acute hypophosphataemia and outcome is poorly understood. Acute hypophosphataemia due to phosphate redistribution alone may have little consequence in the absence of phosphate depletion.[1] Its cause-and-effect relationship with morbidity and mortality has been difficult to establish.[16]

Several studies have reported an association between hypophosphataemia and increased mortality. For example, Shor and colleagues studied 55 patients with sepsis and defined severe hypophosphataemia as iP_{min} (lowest measured phosphate level) < 1 mg/dL (0.32 mmol/L).[19] They found that severe hypophosphataemia during the ICU stay occurred in 47.3% of patients. Those with severe hypophosphataemia had significantly higher mortality rates (80.8% v 34.5%). Zazzo and colleagues prospectively investigated 208 patients admitted to a surgical ICU, and defined hypophosphataemia as $iP_{min} < 0.8$ mmol/L.[7] They found that hypophosphataemia occurred in 28.8% of cases and that mortality was higher in the hypophosphataemic group (30% v 15.2%). Sankaran and colleagues studied 302 patients with bacterial pneumonia admitted to the ICU,[20] and defined hypophosphataemia as $iP_{min} \leqslant 2.4$ mg/dL (0.77 mmol/L) and found that hypophosphataemia occurred in 44.7% of cases. Patients with hypophosphataemia had higher mortality rates (31.9% v 13.2%).

All these studies were small, used different definitions of hypophosphataemia and did not assess the independent relationship between hypophosphataemia and outcome after the necessary adjustments for illness severity. A recent study of a cohort of ICU patients treated with CRRT has so far assessed the independent association between hypophosphataemia and mortality.[21] Similarly to our study, it found no association between hypophosphataemia and mortality after adjustment for illness severity. In that study, on univariate analysis, mortality was lower in patients who experienced hypophosphataemia, as was the case in our study. This single-centre study found an independent association between hypophosphataemia and an increased risk of tracheostomy in only 321 patients treated with CRRT.[21] Finally, a recent large study of 2730 critically ill patients also found no independent relationship between hypophosphataemia and patient outcome.[22]

We also observed a greater incidence of hypophosphataemia in women. It is unclear whether this phenomenon relates to decreased bone mass in women compared with men, whether the "normal" range of phosphate fails to

represent a true normal for postmenopausal women, or if other factors explain this difference. The additional association between caloric intake and persistent hypophosphataemia is in keeping with expectations in patients at high risk of refeeding syndrome.

These observations create uncertainty about the possible impact of hypophosphataemia on outcome in patients with severe AKI. This is particularly problematic in patients receiving CRRT because recent large trials have shown that hypophosphataemia is particularly common in such patients.[11,12] A very recent study from China assessed the relationship between hypophosphataemia and outcome in a cohort of 760 patients treated with CRRT,[23] and no relationship between the incidence of hypophosphataemia and 28-day mortality was found.

Significance of findings

Our study supports the view that, in AKI patients receiving CRRT, hypophosphataemia is especially common when increased intensity of CRRT is applied. By assessing, for the first time, the relationship between hypophosphataemia and patient outcomes with a prospective, detailed data collection within a large cohort of patients treated with CRRT, our study provides strong evidence that hypophosphataemia has no independent association with outcomes. These observations do not support the notion that the lack of difference in outcome between high-intensity and low-intensity CRRT seen in two recent pivotal, randomised controlled trials of dialysis intensity might have been partly due to the adverse effects of more frequent hypophosphataemia in the high-intensity cohort.

Strengths and limitations

We report observational findings from the largest randomised controlled study of CRRT to date. The data were prospectively collected with specific attention to hypophosphataemia. Phosphate levels were measured daily and independently monitored for accuracy for more than 14 000 measurements, the largest assessment of serum phosphate levels to date. They provide the most comprehensive multicentre description of the epidemiology of hypophosphataemia during CRRT and of its association with outcome to date. Patients had detailed outcome data collected with primary outcome assessment at 90 days. We also had, for all patients, demographic, illness severity and biochemical data that were prospectively collected at baseline and could be used in multivariable models to adjust any association of hypophosphataemia according to baseline patient characteristics. The extent of such detail is much greater than anything previously used for analysis in this field.

On the other hand, data were only available from the time of randomisation. At that time, baseline phosphate levels were lower in patients who subsequently had one or more episodes of hypophosphataemia. It is possible that hyperphosphataemia at randomisation reflected disease severity in a way that was not captured by illness severity scores, and this difference partly explains our findings that patients with hypophosphataemia appeared to do better. Joint modelling analysis found an independent association between hyperphosphataemia during the observation period and mortality. Extended knowledge of phosphate levels before randomisation might then be particularly useful in increasing the validity of our observations. However, we cannot provide information on hypophosphataemia in the days before randomisation. In the RENAL trial, the time between ICU admission and randomisation was more than 2 days, and the mean duration of study time was about 13 days, suggesting that the evolution of serum phosphate levels in the prerandomisation period was unlikely to materially affect the study findings.

The findings of our study are open to interpretation because of the competing effect of mortality with hypophosphataemia (patients who stay in ICU longer are both more likely to live and to experience an episode of hypophosphataemia). However, after excluding patients who died in the first 96 hours or 7 days (when the vast majority of hypophosphataemic episodes had occurred), no independent relationship between hypophosphataemia and outcome could be confirmed. Sensitivity analyses and competing risk analyses all confirmed these findings.

We did not have data on the treatment of hypophosphataemia. However, current practice in Australia and New Zealand ICUs is to administer intravenous phosphate in response to hypophosphataemia,[25,26] as is current practice elsewhere.[24] As hypophosphataemia is unlikely to self-correct, and as it was typically returned to normal within 24 hours in most cases, such treatment can be assumed to have been given to most patients.

Therefore, our results do not imply that hypophosphataemia is of little consequence and should not be corrected. Although it may not carry a statistical association with increased mortality, its development is not desirable and our findings occurred in a clinical environment where treatment was applied. Our findings imply instead that, in a clinical setting where the occurrence of hypophosphataemia is detected by at least daily measurement and its levels corrected by phosphate supplementation, no independent relationship can be identified between hypophosphataemia and increased risk of death. Another potential aspect of our findings is that hypophosphataemia associated with CRRT-induced phosphate losses may have different implications than disease-induced hypophosphataemia.

Conclusions

In the RENAL study, in a clinical environment where hypophosphataemia was generally corrected by phosphate administration, patients with hypophosphataemia had a lower unadjusted mortality rate than those without an episode of hypophosphataemia. Surviving patients had a greater incidence of hypophosphataemia. After correction for multiple confounding variables and the application of different statistical modelling techniques, including time-adjustment, competing risk adjustment, joint modelling, Cox proportional hazards modelling and sensitivity analyses, this favourable association could not be confirmed. Thus, until higher level evidence emerges, hypophosphataemia cannot be considered a major risk factor for increased mortality in patients treated with CRRT. Perhaps, more importantly, the greater incidence of hypophosphataemia during high-intensity CRRT is unlikely to have negatively affected the outcome of these patients during the RENAL trial.

Competing interests

Rinaldo Bellomo has received consulting fees as advisor for Gambro. No other potential conflict of interest relevant to this article was reported.

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Appendix 1. Randomised Evaluation of Normal vs Augmented Level (RENAL) Replacement Therapy Study committees, teams, site investigators and research coordinators (alphabetical order)

The 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.

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Appendix 2. Table 2a. Multivariate logistic regression of hypophosphataemia* during intensive care unit stay

Variable and effect (discrete variable)	Odds ratio	95% CI	*P*
Treatment, high intensity v low intensity	0.659	0.46–0.94	0.0229
Mean daily calorie intake (per 500 kcal)	1.781	1.51–2.1	< 0.0001
Mean daily fluid balance (L)	0.626	0.48–0.81	0.0004
Positive mean fluid balance, yes v no	1.874	1.11–3.17	0.0192
Fluid overload at randomisation, yes v no	0.941	0.65–1.36	0.7471
Sex, male v female	0.557	0.38–0.81	0.0022
Severe sepsis at baseline, yes v no	0.983	0.67–1.45	0.9321
APACHE III score	1.009	1–1.02	0.0307
SOFA score			
Respiration, failure v dysfunction	0.244	0.03–1.98	0.1864
Respiration, normal v dysfunction	0.214	0.04–1.03	0.0550
Cardiovascular, failure v dysfunction	1.981	0.96–4.1	0.0655
Cardiovascular, normal v dysfunction	1.347	0.61–2.98	0.4625
Renal, failure v dysfunction	1.106	0.69–1.76	0.6718
Renal, normal v dysfunction	0.978	0.29–3.33	0.9719
Overall (sum of all non-missing organ scores/5)	0.945	0.58–1.55	0.8217
⩾ 1 non-renal organ failure (SOFA score 3–4), yes v no	0.632	0.25–1.59	0.3288
Last serum urea before randomisation (mmol/L)	0.972	0.83–1.14	0.7224
Last creatinine before randomisation (μmol/L)	1.009	1–1.02	0.0700
Potassium (mmol/L)	0.673	0.53–0.85	0.0009
Chloride (mmol/L)	1.001	0.97–1.03	0.9615
Bicarbonate (mmol/L)	0.971	0.93–1.01	0.1649
Urea (mmol/L)	0.991	0.85–1.16	0.9066
Creatinine (μmol/L)	0.992	0.98–1	0.0979
Albumin (g/L)	1.019	0.99–1.05	0.1750
pH	0.345	0.06–2.11	0.2491
Mechanical ventilation, yes v no	2.457	0.32–19	0.3894
Estimated glomerular filtration rate > 60 mL/min, yes v no	1.056	0.71–1.56	0.7863

APACHE = Acute Physiology and Chronic Health Evaluation.
SOFA = sequential organ failure assessment. * Hypophosphataemia defined as a single episode of phosphate concentration < 0.6 mmol/L.

Appendix 2. Table 2b. Multivariate logistic regression for the prediction of persistent hypophosphataemia*

Variable and effect (discrete variable)	Odds ratio	95% CI	*P*
Treatment, high intensity v low intensity	0.574	0.34–0.96	0.0328
Sex, male v female	0.467	0.28–0.79	0.0041
Mean daily calorie intake (/500 kcal)	1.646	1.31–2.07	< 0.0001

APACHE = Acute Physiology and Chronic Health Evaluation. SOFA = sequential organ failure assessment. * Only variables with $P < 0.05$ reported; other variables included treatment, mean daily calorie intake, mean daily fluid balance, positive mean fluid balance, fluid overload at randomisation, sex, severe sepsis at baseline, APACHE III score, SOFA respiratory, cardiovascular and renal scores, ⩾ 1 non-renal organ failure, urea, creatinine, potassium, bicarbonate, albumin, magnesium, pH level at randomisation, mechanical ventilation, estimated glomerular filtration rate.

Appendix 3. Table 3a. Multivariate logistic regression for 90-day mortality (all patients)*

Variable and effect (discrete variable)	Odds ratio	95% CI	*P*
Intercept	NA	NA	0.8154
Hypophosphataemia, yes v no	0.562	0.41–0.77	0.0003
Mean fluid balance, input–output (L)	1.998	1.58–2.53	< 0.0001
Patient age, years	1.038	1.03–1.05	< 0.0001
Patient weight, kg	0.987	0.98–1	0.0186
Time from ICU admission to randomisation, days	1.002	1–1	0.0087
Severe sepsis at baseline, yes v no	1.283	0.95–1.72	0.0992
SOFA liver score, failure v normal	3.431	1.56–7.55	0.0022
International normalised ratio	1.21	1.04–1.41	0.0141
Albumin (g/L)	0.976	0.96–1	0.0249

NA = not applicable. ICU = intensive care unit. SOFA = sequential organ failure assessment. * Only variables with $P < 0.05$ reported; other variables included treatment, mean daily calorie intake, mean daily fluid balance, positive mean fluid balance, fluid overload at randomisation, sex, severe sepsis at baseline, APACHE III score, SOFA respiratory, cardiovascular and renal scores, ⩾ 1 non-renal organ failure, urea, creatinine, potassium, bicarbonate, albumin, magnesium, pH level at randomisation, mechanical ventilation, estimated glomerular filtration rate.

Appendix 3. Table 3b. Multivariable logistic regression for 90-day mortality (patients who lived > 96 hours)*

Variable and effect (discrete variable)	Odds ratio	95% CI	*P*
Intercept	NA	NA	0.4324
Hypophosphataemia, yes v no	0.77	0.56–1.07	0.1149
Mean fluid balance, input–output (L)	1.595	1.21–2.11	0.001
Patient age, years	1.042	1.03–1.05	< 0.0001
Time from ICU admission to randomisation, days	1.002	1–1	0.0202
SOFA liver score, failure v normal	3.234	1.38–7.59	0.007
International normalised ratio	1.224	1.05–1.43	0.0094
Haemoglobin (g/L)	0.991	0.98–1	0.049

NA = not applicable. ICU = intensive care unit. SOFA = sequential organ failure assessment. * Only variables with $P < 0.05$ reported; other variables included treatment, mean daily calorie intake, mean daily fluid balance, positive mean fluid balance, fluid overload at randomisation, sex, severe sepsis at baseline, APACHE III score, SOFA respiratory, cardiovascular and renal scores, ⩾ 1 non-renal organ failure, urea, creatinine, potassium, bicarbonate, albumin, magnesium, pH level at randomisation, mechanical ventilation, estimated glomerular filtration rate.

Appendix 3. Table 3c. Multivariable logistic regression for 90-day mortality (patients who lived > 7 days)*

Variable and effect (discrete variable)	Odds ratio	95% CI	*P*
Intercept	NA	NA	0.581
Hypophosphataemia, yes v no	0.822	0.58–1.16	0.2668
Mean fluid balance, input–output (L)	1.731	1.27–2.36	0.0005
Patient age, years	1.039	1.03–1.05	< 0.0001
Patient weight, kg	0.986	0.97–1	0.03
Time from ICU admission to randomisation, days	1.002	1.00–1	0.0358
SOFA liver score, failure v normal	3.778	1.50–9.51	0.0048
International normalised ratio	1.181	1.01–1.38	0.0351
Haemoglobin (g/L)	0.989	0.98–1	0.0204

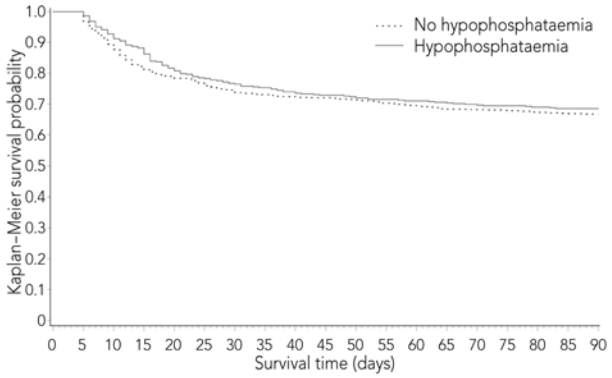
NA = not applicable. ICU = intensive care unit. SOFA = sequential organ failure assessment. * Only variables with $P < 0.05$ reported; other variables included treatment, mean daily calorie intake, mean daily fluid balance, positive mean fluid balance, fluid overload at randomisation, sex, severe sepsis at baseline, APACHE III score, SOFA respiratory, cardiovascular and renal scores, ⩾ 1 non-renal organ failure, urea, creatinine, potassium, bicarbonate, albumin, magnesium, pH level at randomisation, mechanical ventilation, estimated glomerular filtration rate.

Appendix 4. Sensitivity analysis: Cox model regression, death at Day 90*

Variable	Hazard ratio**	95% CI**	*P***
Hypophosphataemia, yes v no	0.631	(0.441–0.903)	0.0117
Calorie intake (per 500 kcal)	1.231	(1.066–1.422)	0.0046
Mean daily fluid balance (L)	1.536	(1.199–1.967)	0.0007
Positive mean fluid balance, yes v no	0.932	(0.609–1.426)	0.7442
Fluid overload at randomisation, yes v no	0.815	(0.605–1.099)	0.1797
Patient age	1.016	(1.004–1.029)	0.0115
Sex, male v female	1.086	(0.786–1.501)	0.6158
Severe sepsis at baseline	1.215	(0.879–1.680)	0.2376
APACHE III score	1.010	(1.003–1.016)	0.0034
SOFA respiration score, failure v dysfunction	3.379	(0.631–18.09)	0.1549
SOFA respiration score, normal v dysfunction	1.188	(0.494–2.856)	0.7001
SOFA cardiovascular score	0.869	(0.772–0.977)	0.0190
SOFA renal score, failure v dysfunction	0.764	(0.528–1.105)	0.1525
SOFA renal score, failure v dysfunction	0.818	(0.195–3.425)	0.7833
⩾ 1 non-renal organ failure (SOFA score 3–4), yes v no	1.377	(0.676–2.808)	0.3784
Last serum urea before randomisation (mmol/L)	1.036	(0.947–1.134)	0.4359
Last creatinine before randomisation (μmol/L)	0.998	(0.996–1.001)	0.1844
Potassium (mmol/L)	0.917	(0.762–1.102)	0.3553
Chloride (mmol/L)	0.983	(0.961–1.005)	0.1226
Bicarbonate (mmol/L)	0.989	(0.958–1.021)	0.4879
Urea (mmol/L)	0.988	(0.904–1.081)	0.8001
Creatinine (μmol/L)	1.000	(0.998–1.002)	0.8910
Albumin (g/L)	0.993	(0.972–1.015)	0.5407
Magnesium (mmol/L)	1.577	(1.075–2.312)	0.0197
pH	0.932	(0.239–3.629)	0.9193
Mechanical ventilation, yes v no	0.334	(0.066–1.693)	0.1853
Estimated glomerular filtration rate > 60 mL/min	0.961	(0.689–1.341)	0.8164

APACHE = Acute Physiology and Chronic Health Evaluation. SOFA = sequential organ failure assessment. * Adjusted for hypophosphataemia (yes/no) during study treatment; only patients who survived > 96 hours were included; model stratified by treatment allocation (intensive or conventional). ** Adjusted model; covariates for adjusted model include calorie intake, mean daily fluid balance, positive v negative fluid balance and oedema; baseline characteristics include patient age, sex, intensive care unit admission status (operative or non-operative), sepsis (yes or no), APACHE III score, organ failure (respiratory, coagulation, liver, cardiovascular or renal SOFA score) and prerandomisation blood phosphate concentration dichotomised at the median value.

Appendix 5. Kaplan–Meier curve for hypophosphataemia v no hypophosphataemia, excluding patients who died in the first 96 hours



Chapter 10

Calorie intake and patient outcomes in severe acute kidney injury: findings from the Randomized Evaluation of Normal vs. Augmented Level of Replacement Therapy (RENAL) study trial

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Calorie intake and patient outcomes in severe acute kidney injury: findings from The Randomized Evaluation of Normal vs. Augmented Level of Replacement Therapy (RENAL) study trial

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Abstract

Introduction: Current practice in the delivery of caloric intake (DCI) in patients with severe acute kidney injury (AKI) receiving renal replacement therapy (RRT) is unknown. We aimed to describe calorie administration in patients enrolled in the Randomized Evaluation of Normal vs. Augmented Level of Replacement Therapy (RENAL) study and to assess the association between DCI and clinical outcomes.

Methods: We performed a secondary analysis in 1456 patients from the RENAL trial. We measured the dose and evolution of DCI during treatment and analyzed its association with major clinical outcomes using multivariable logistic regression, Cox proportional hazards models, and time adjusted models.

Results: Overall, mean DCI during treatment in ICU was low at only 10.9 ± 9 Kcal/kg/day for non-survivors and 11 ± 9 Kcal/kg/day for survivors. Among patients with a lower DCI (below the median) 334 of 729 (45.8%) had died at 90-days after randomization compared with 316 of 727 (43.3%) patients with a higher DCI (above the median) ($P = 0.34$). On multivariable logistic regression analysis, mean DCI carried an odds ratio of 0.95 (95% confidence interval (CI): 0.91-1.00; $P = 0.06$) per 100 Kcal increase for 90-day mortality. DCI was not associated with significant differences in renal replacement (RRT) free days, mechanical ventilation free days, ICU free days and hospital free days. These findings remained essentially unaltered after time adjusted analysis and Cox proportional hazards modeling.

Conclusions: In the RENAL study, mean DCI was low. Within the limits of such low caloric intake, greater DCI was not associated with improved clinical outcomes.

Trial registration: ClinicalTrials.gov number, NCT00221013

Introduction

Achieving an adequate daily calorie intake (DCI) is widely considered beneficial in critically ill patients in general and in particular in patients with acute kidney injury (AKI) [1]. Guidelines recommend the early administration of enteral nutrition whenever possible to achieve an energy intake of 25 to 35 Kcal/day and consideration of parenteral nutrition when enteral nutrition cannot achieve such calorie intake goals [2-4]. However, despite the above guidelines, there is also concern that the administration of energy at such levels in critically ill patients may not be advantageous [5]. Some investigators have shown that low calorie nutrition alone may be sufficient [6] or even desirable [7].

In severe AKI patients who require continuous renal replacement therapy (CRRT), there are very limited data on current practice or on the association between energy intake and patient-centered outcomes. In this setting, all studies are almost 20 years old, single center in design, small in size and with replacement fluid or dialysate fluids rich in glucose and/or lactate [8-11]. Such practices are not relevant to modern CRRT [12-14]. Finally, the impact

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of CRRT itself on caloric expenditure remains controversial as it may both lead to decreased energy expenditure through cooling; increased loss of energy as patients seek to maintain body temperature in the presence of an extracorporeal circuit, or nutrient loss across the filter [15,16].

The Randomized Evaluation of Normal vs. Augmented Level of Replacement Therapy (RENAL) study [17-20], offers a unique opportunity to explore the association between DCI and outcome because of its size and the availability of detailed DCI data. Accordingly, we conducted a secondary analysis of the RENAL study findings to describe current DCI practice in such patients and study the association between DCI and clinical outcomes.

Methods

The RENAL study was a multicenter, prospective, randomized trial of two levels of intensity of CRRT in 1,508 critically ill patients with AKI conducted in 35 ICUs in Australia and New Zealand [17,21]. The Human Research Ethics Committees of the University of Sydney and all participating institutions approved the study (Additional file 1 provides a list of the institutional review boards that approved the study). Written informed consent was obtained from patients or their person responsible.

The methodological details of the RENAL study were recently reported [17]. In brief, patients were eligible for enrollment if they were critically ill adults who had AKI, were deemed by the treating clinician to require RRT and fulfilled predefined criteria. Eligible patients were randomly assigned to continuous veno-venous hemodiafiltration (CVVHDF) with effluent flow at 40 ml/Kg/hr (higher intensity) or 25 ml/Kg/hr (lower intensity). Study treatment was discontinued on death, discharge from ICU, or recovery of renal function. The primary study end point was death from any cause by day 90.

Daily calorie intake

The study did not prescribe any nutritional intake protocol. Nutritional therapy was left to the discretion of attending clinicians. In all patients, DCI was calculated as the sum of all calories administered each day with the exclusion of protein nitrogen. For each patient a mean was calculated during the study period using the DCI value for each day. For the purpose of the study, calorie intake included: a) all glucose given parenterally as part of either drug infusions in 5% glucose or maintenance fluid containing glucose; b) any parenteral nutrition; c) all lipids administered as part of parenteral nutritional solutions, and d) all carbohydrate or lipid-derived calories administered as enteral nutritional solutions. Propofol intake was taken into account. According to the study protocol, DCI data were obtained until the first occurrence of either death, or ICU discharge or the completion of 28 days from study randomization (study treatment period).

Statistical analysis

Continuous variables were expressed as means with SD for normally distributed variables and as median and IQR for non-normally distributed variables. Comparisons were made using the Student *t*-test or the Mann-Whitney test where appropriate. We divided patients into two groups according to mean DCI calculated for each patient during the study period, low DCI when the individual mean DCI was lower than the median value for the study population and high DCI when individual mean DCI was greater than the median value. Patients with lower and higher DCI were compared by univariate analysis. We then compared the DCI of survivors and non-survivors for DCI and the progressive change over time in DCI. Mean DCI-related variables (dichotomized and continuous) were then assessed for their independent relationship with survival by multivariable logistic regression analysis with adjustment for co-linearity and with adjustment for the following variables: treatment group, acute physiology and chronic health evaluation (APACHE) III score, APACHE III diagnostic groups, daily use of CRRT, age, time from ICU to randomization, presence of sepsis, sequential organ failure assessment (SOFA) respiratory score, SOFA coagulation score, SOFA liver score, SOFA cardiovascular score, SOFA renal score, presence of non-renal organ failure, international normalized ratio (INR) for prothrombin time, activated partial thromboplastin time (APPT), platelet count, serum creatinine, arterial partial pressure of oxygen/inspired oxygen fraction (PaO2/FiO2) ratio, tension of carbon dioxide in arterial blood (PaCO2), pH, glucose, albumin, hemoglobin, use of mechanical ventilation, mean daily fluid balance, and clinical diagnosis of significant edema at randomization.

Multivariable linear regression analysis was similarly used to assess the relationship between individual mean DCI and mechanical ventilation-free days; RRT-free days; ICU-free days and hospital-free days at 90 days, as the dependent variables. Unadjusted analysis of time to death within 90 days of randomization used the Kaplan-Meier product limit estimates and compared survival curves using the log-rank test. To assess whether post-ICU treatment might have affected our findings, we also estimated the relationship between DCI and mortality censored at 28 days or ICU discharge. To test the robustness of any association between mortality and DCI, additional models were applied to data analysis. Such multivariable models included time-adjusted modeling with a cut off of 96 hrs (to exclude patients who died before full nutrition was achieved) and Cox proportional hazards modeling applying the same adjustments for variables included in the logistic regression model. A two-sided P-value <0.05 was taken to indicate statistical significance. Statistical analyses were performed and independently checked with the use of SAS software, version 9.1.

Results

Of the 1,508 patients enrolled in the RENAL study, complete DCI data were available for 1,456 (96.6%). The characteristics of study patients according to whether they received low or high amounts of DCI are compared in Table 1 and are significantly different between the two groups.

Among patients with a low mean DCI, 334 of 729 (45.8%) had died 90 days after randomization, compared with 316 of 727 (43.3%) patients who received a mean DCI above the median value ($P = 0.34$). Moreover, mean DCI was 867 Kcal/day, with a value among non-survivors of 847 Kcal/day (10.9 Kcal/Kg/day) compared with 883 Kcal/day (11.0 Kcal/Kg/day) among survivors ($P = 0.32$) (Table 2). Mean calorie to protein ratio was 24.9, with a value of among non-survivors of 25.2 compared with 24.7 among survivors ($P = 0.39$).

Overall, 874 patients received enteral nutrition only on 8,334 study days (69.1%), and 382 patients received parenteral nutrition only for a total of 1,667 (13.8%) study days and 200 patients received a combination of enteral and parenteral nutrition for a total of 2,055 (17.1%) study days. The daily DCI for survivors and non-survivors for the first 14 days of observation is displayed in Figure 1. DCI in both groups tended to increase over time reaching a near plateau after approximately 96 hrs. The unadjusted time-to event analysis is shown in Figure 2a for all patients and in Figure 2b after removing patients who died in the first 96 hrs.

On multivariable logistic regression analysis, only a few variables remained independently associated with 90-day mortality (Table 3). Importantly, increased daily DCI during study treatment was not independently associated with decreased mortality. On multivariable linear regression analysis, DCI also showed no association with decreased RRT-free days at day 90 after randomization. When the outcome was survival at 28 days or ICU discharge, there was still no association between DCI above the median value and outcome (odds ratio (OR) 1.02; 95% CI 0.61, 1.71; $P = 0.93$). When a DCI >25 Kcal/Kg/day was used to indicate adequate calorie intake, no significant association was found (OR 0.93; 95% CI 0.47, 1.72; $P = 0.75$). Similar findings were seen when the outcomes of interest were RRT-free days, ICU-free days or hospital-free days (Table 4a, b, c).

The association of DCI with outcomes was also tested by means of additional time-adjusted modeling (1,183 patients were still alive after 96 hrs) and Cox proportional hazards modeling. Both modeling approaches confirmed the main study findings (see Additional file 2).

Discussion

Statement of key findings

We used data from a multicenter, randomized, controlled trial of the intensity of CRRT in critically ill patients with AKI to describe current calorie administration practice and to assess the association between DCI and clinical outcomes. We found that overall mean DCI was low at approximately 11 Kcal/Kg/day. In addition, we found that patients with a high DCI (above the median) had similar mortality to patients with a low DCI (below the median). Finally, non-survivors had a similar DCI to survivors. When we estimated the independent association between DCI and outcome at day 90, a high DCI was not independently associated with a significant decrease in the OR for 90-day mortality. To further test the robustness of this finding we performed additional time-adjusted analyses and Cox proportional hazards modeling. These analyses found no independent association between DCI and 90-day mortality or other clinical outcomes.

Comparison with previous studies

No other studies have reported current calorie delivery practice in patients with AKI. In general critically ill patients however, a recent multicenter observational study in 167 ICU's found that mean DCI was 14 Kcal/Kg/day [22], a value only slightly above that found in our study. In a recent multicenter trial of intensive insulin therapy in critically ill patients [23], mean DCI was approximately 11 Kcal/Kg/day, a value identical to that delivered to our patients. Thus, current calorie administration practice in Australia and New Zealand (ANZ) is similar to current ICU practice worldwide. In the multicenter observational study of nutrition in general ICU patients cited above, greater mean DCI appeared associated with improved survival. However, no adjustment was made for the competing risk of death [24]. Such bias can be clearly demonstrated in critically ill patients [23,25] where mean DCI increases with time. Thus, patients who die early inevitably receive fewer calories. This pattern creates an artificially inflated chance of an apparent association between greater mean DCI and survival.

Authors [26] and guidelines [3,4,27] continue to recommend a DCI of at least 25 to 35 Kcal/Kg/day in AKI patients, yet, the evidence supporting such recommendations is weak and based on small to very small single-center studies with physiological outcomes only. Moreover, although such recommendations appear reasonable from a physiological and energy expenditure grounds [28-30], no randomized controlled trials (RCTs) exist to compare, for example 10 Kcal/Kg/day (current practice) to 30 Kcal/Kg/day (recommended practice) of energy intake in AKI patients. In support of the need for RCTs, recent investigations have found that permissive underfeeding, trophic feeding or delayed parenteral feeding may be equivalent or perhaps even superior to currently recommended approaches [5-7,25].

Table 1 Comparison of baseline characteristics for patient with low (below median) and high (above median) mean daily calorie intake (DCI)

Baseline characteristics	Low DCI, n = 729	High DCI, n = 728	*P*-value
Age	65.4 (14.8)	64.7 (14.9)	0.022
Male sex	457 (62.7%)	484/728 (66.5%)	0.129
eGFR	53.0 (30.9)	60.1 (30.7)	0.001
Mechanical ventilation	437 (59.9%)	639 (87.8%)	<0.001
Severe sepsis at baseline	307 (42.1%)	412 (56.6%)	<0.001
APACHE III score	103.4 (25.8)	101.5 (25.6)	0.163
SOFA cardiovascular	2.7 (1.6)	3.0 (1.4)	<0.001
SOFA respiration (score)	2.5 (1.1)	3.0 (0.7)	<0.001
SOFA coagulation (score)	0.8 (1.1)	1.1 (1.2)	<0.001
SOFA liver (score)	0.9 (1.2)	1.0 (1.1)	0.300
Weight	79.9 (12.8)	81.4 (13.0)	0.029
Source of admission			
Accident and emergency department	187/686 (27.3%)	161/679 (23.7%)	0.003
Hospital floor/ward	215/686 (31.3%)	172/679 (25.3%)	
Transfer from another ICU	43/686 (6.3%)	66/679 (9.7%)	
Transfer from another hospital	65/686 (9.5%)	89/679 (16.6%)	
Operating room/recovery after emergency surgery	91/686 (13.3%)	113/679 (11.5%)	
Operating room/recovery after elective surgery	85/686 (12.4%)	78/679 (14.1%)	
Non-operative admission diagnosis			
Cardiovascular	245/536 (45.7%)	287/510 (56/3%)	<0.001
Genitourinary	177/536 (33.0%)	52/510 (10.2%)	
Gastrointestinal	39/536 (7.3%)	36/510 (7.1%)	
Hematology	10/536 (1.9%)	12/510 (2.4%)	
Metabolic/endocrine	14/536 (2.6%)	11/510 (2.2%)	
Neurologic	4/536 (0.7%)	6/511 (1.2%)	
Respiratory	43/536 (8.0%)	103/511 (20.2%)	
Transplant	4/536 (0.7%)	1/511 (0.2%)	
Trauma	0/536 (0.0%)	2/511 (0.4%)	
Operative admission diagnosis			
Cardiovascular	131/193 (67.9%)	137/218 (62.8%)	0.256
Genitourinary	3/193 (1.6%)	1/218 (0.5%)	
Gastrointestinal	39/193 (20.2%)	57/218 (26.1%)	
Neurologic	3/193 (1.6%)	4/218 (1.8%)	
Respiratory	3/193 (1.6%)	5/218 (2.3%)	
Transplant	7/193 (3.6%)	2/218 (0.9%)	
Trauma	7/193 (3.6%)	12/218 (5.5%)	
Plasma urea (mmol/L)	23.7 (13.8)	23.3 (11.7)	0.542
Creatinine at randomization (μmol/L)	369 (231)	300 (142)	<0.001
pH	7.2 (0.1)	7.3 (0.1)	<0.001
Bicarbonate (mmol/L)	17.1 (5.8)	19.5 (5.6)	<0.001
Base excess (mEql/L)	−9.7 (6.9)	−6.9 (6.7)	<0.001

Continuous variables expressed as mean with standard deviation in brackets. Nominal variables expressed as number with percentage in brackets. SOFA, sequential organ failure score; RRT, renal replacement therapy; MV, mechanical ventilation; APACHE, acute physiology and chronic health evaluation; eGFR, estimated glomerular filtration rate.

Table 2 Daily calorie intake (DCI) according to survival status at 90 days after randomization

Baseline characteristics	Non-survivors, n = 654	Survivors, n = 810	*P*-value
Mean DCI during study			
Number	649	807	0.3185
Mean calories (SD)	846.7 (681)	883.3 (709)	
Q1 Q2 Q3	148.0 839.7 1412	90.0 905.8 1447	
Missing	5	3	
Weight-adjusted mean DCI during study			
Number	649	807	0.8086
Mean calories/kg (SD)	10.9 (9.0)	11.0 (9.0)	
Q1 Q2 Q3	1.7 10.4 17.4	1.1 11.2 17.6	
Missing	5	3	

Refers to index admission to a maximum of 28 days (trial treatment); weight-adjusted DCI/patient weight in Kg; Q, quartile.

Significance of study findings

These findings from the RENAL study provide the first data on current nutritional practice in patients with severe AKI. They also provide novel information on the relationship between mean DCI and outcome. Such information was collected as part of large multicenter study with independent data verification and negligible missing data. They also provide such information in the setting of essentially exclusive CRRT use. This difference is important because intermittent hemodialysis (IHD) has been shown to limit the ability to control volume status and uremia in critically ill patients with AKI [29,31], thereby potentially impeding full nutritional intake. On the other hand, with CRRT, volume control and full nutritional therapy are free of the limitations imposed by IHD. Thus, given that fluid accumulation is not a problem, mean DCI in this setting can be logically taken to reflect therapeutic choices rather than technical limitations.

Our study demonstrates that mean DCI was well below guideline-based targets in patients receiving CRRT. By assessing, for the first time, its relationship with patient outcomes in the setting of prospective and detailed data collection within a large cohort of patients treated with CRRT, our study also provides evidence that within the range of mean DCI provided in this study, there was no robust independent association between greater mean DCI and favorable outcome, including 90-day mortality and other patient-centered outcomes such as mechanical ventilation, ICU- and hospital-free days. In fact, after early deaths were excluded, patients with a DCI above the median were more likely to die. This surprising finding is possibly due to the confounding effect of time (DCI increases with time and patients who are still in ICU as time goes by have failed to improve and are thus more likely to die) but, nonetheless, highlights the lack of a robust and unchanging relationship with DCI which, if present, may be expected to overcome the effect of confounding.

Our findings may provoke further debate on whether caloric intake is an important determinant of outcome; whether caloric targets as set by current guidelines are justified and whether more restrictive approaches may be acceptable or even desirable. The mechanism responsible for the failure of enhanced nutritional intake to change patient outcome may be complex and may depend on both anabolic resistance [32] and in AKI patients, on

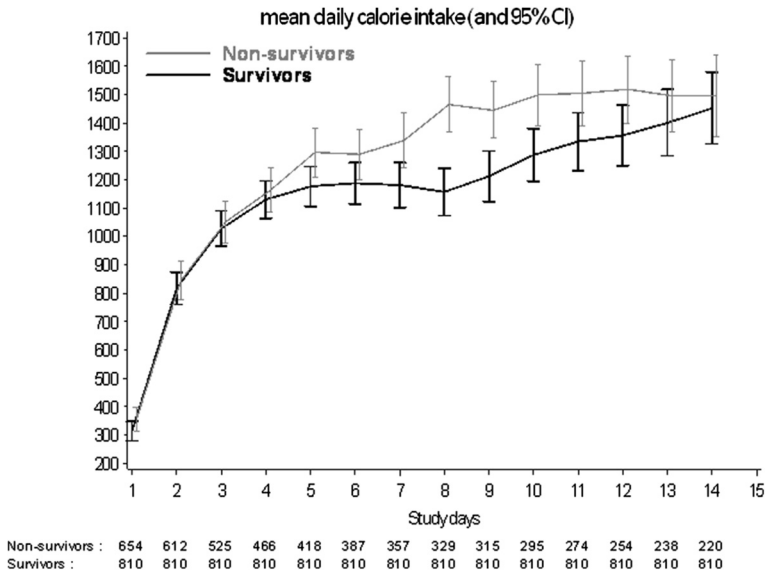

Figure 1 Graphic representation of mean daily caloric intake (DCI) over the first 2 weeks of observation after randomization according to survival status at 90 days.

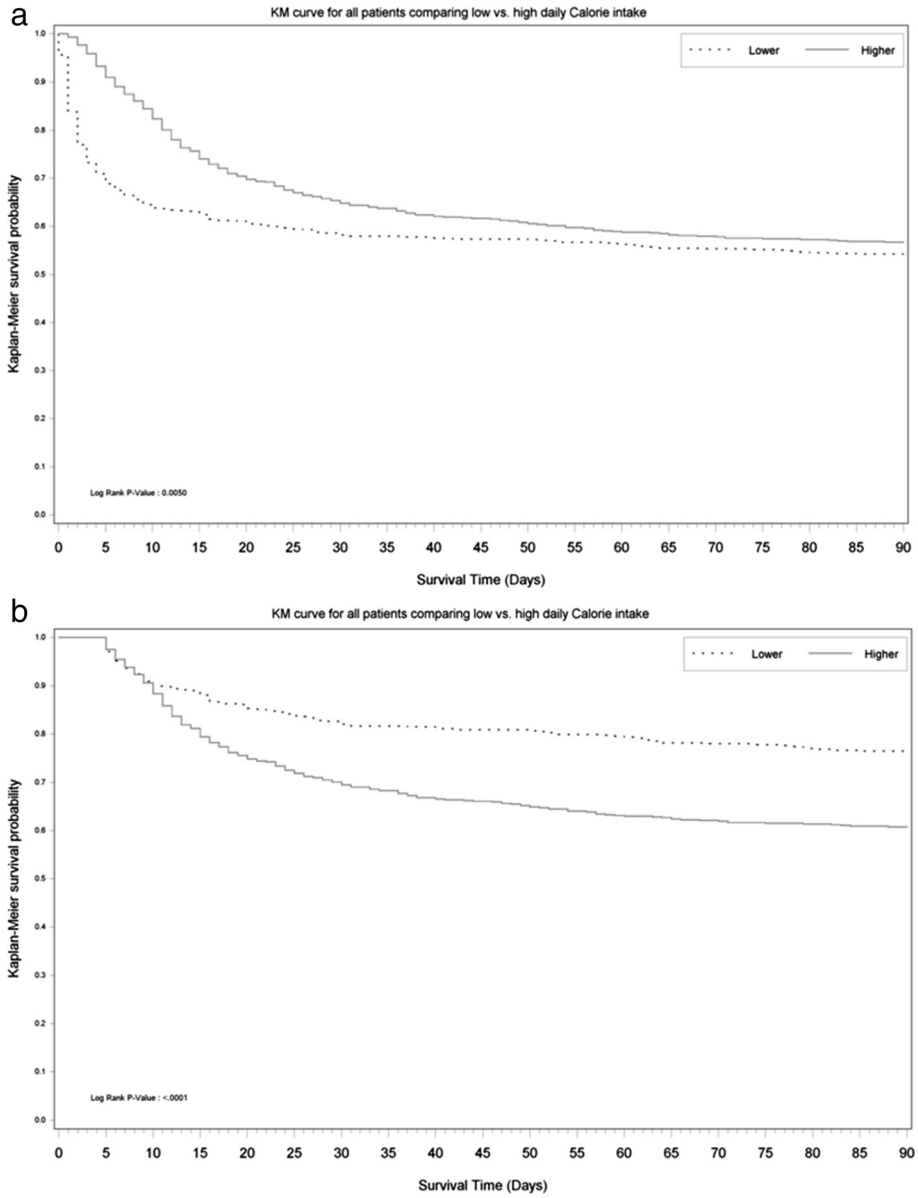

Figure 2 Kaplan-Meier plots before and after excluding early deaths. (a) Kaplan-Meier graph of survival plots from randomization to day 90 stratified by the delivery of lower (below median) or higher (above median) daily calorie intake (DCI) during the index ICU admission. No *P*-values are provided as the plot is not adjusted for confounders and is shown to emphasize the reversal of the curve (see Figure 2b) once early deaths are excluded. **(b)** Kaplan-Meier graph of survival plots from randomization to day 90 stratified by the delivery of lower (below median) or higher (above median) DCI during the index ICU admission, after exclusion of patients who died in the first 96 hrs. No *P*-values are provided as the plot is not adjusted for confounders and is shown to emphasize the reversal of the curves (see Figure 2a) once early deaths are excluded.

the unique changes in protein metabolism seen with this condition [33]. Recent data from randomized controlled trials of nutrition in critically ill patients [5-7,25] also suggest that a more conservative approach to caloric delivery may, at the very least, be safe. Given that severe AKI is relatively common in critically ill patients and given such therapeutic uncertainty, RCTs are urgently needed.

Study strengths and limitations

This study reports observational findings from a large multicenter randomized controlled study of CRRT for AKI. The data were prospectively collected with specific attention to mean DCI and independently monitored for accuracy, and were free of selection bias. As such, they provide the most comprehensive description of mean DCI during CRRT and of its association with outcome to date.

Table 3 Multivariate logistic regression for 90-day mortality

Variable name	Effect (discrete variable)	Odds ratio	CI (95%)	*P*-value
Median daily calorie intake during ICU admission	High versus low	1.079	0.55 2.13	0.8275
Mean daily calorie intake during ICU admission (per 100 Kcal change)		0.953	0.91 1.00	0.0636
Mean fluid balance (input-output) (litre)		2.016	1.61 2.53	<.0001
Patient's age		1.037	1.03 1.05	<.0001
Patient's weight (Kg)		0.989	0.98 1.00	0.0394
Time from ICU admission to randomization (days)		1.002	1.00 1.00	0.0047
SOFA liver (score)	Failure versus normal	3.384	1.55 7.38	0.0022
International normalized ratio		1.200	1.03 1.39	0.0172
Hemoglobin (g/L)		0.992	0.98 1.00	0.0353
Albumin (g/L)		0.977	0.96 1.00	0.0300
PaCO2 (mm/Hg)		1.016	1.00 1.03	0.0249

Daily calorie intake and all variables with $P < 0.05$ presented; APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment; PaCO2, tension of carbon dioxide in arterial blood.

Table 4 Multivariable linear regression for secondary outcomes*

Variable name	Estimate	Standard error	*P*-value
a. Multivariable linear regression for RRT-free days			
Intercept	−40.32510	33.71933	0.2323
Mean daily calorie intake during ICU admission	0.00189	0.00171	0.2695
Median daily calorie intake during ICU admission	−1.09792	2.61145	0.6744
Positive mean fluid balance	−4.09805	0.87492	<.0001
Treatment	−1.97170	0.85163	0.0210
Time from ICU admission to randomization (in days)	−0.01644	0.00469	0.0005
SOFA liver (score)	−1.63540	0.44579	0.0003
APPT	−0.05581	0.02105	0.0083
pH	8.45062	4.27094	0.0484
b. Multivariate linear regression of ICU-free days			
Intercept	−221.76773	281.51940	0.4313
Mean daily calorie intake during ICU admission	0.00468	0.00649	0.4714
Median daily calorie intake during ICU admission	2.89089	8.90361	0.7456
Positive mean fluid balance	−19.69578	3.36383	<.0001
Positive ventilation: no = reference group	−13.45268	5.58339	0.0165
Patient's weight (Kg)	0.45320	0.13896	0.0012
Time from ICU admission to randomization (days)	−0.03736	0.01756	0.0340
Last creatinine concentration	0.11279	0.04434	0.0114
c. Multivariate linear regression of hospital-free days			
Intercept	25.05875	258.60573	0.9229
Mean daily calorie intake during ICU admission	−0.00349	0.00601	0.5625
Median daily calorie intake during ICU admission	2.11260	8.32222	0.7997
Positive mean fluid balance	−16.17529	3.08521	<.0001
Patient's weight (Kg)	0.29499	0.12933	0.0231
Last serum urea concentration	−3.72244	1.85441	0.0454
Last creatinine concentration	0.09767	0.04131	0.0185
Glucose (mmol/L)	1.09456	0.50830	0.0319

*Only DCI related variable and significant variables reported. SOFA, sequential organ failure assessment; activated partial thromboplastin time.

All patients had detailed, prospectively collected outcome data with primary outcome at 90 days. This approach avoided informative censoring of competing events and 90-day mortality is free from ascertainment bias unlike other more subjective primary endpoints (for example, infections) sometimes used in the literature. In addition, all patients had prospectively collected demographic, illness severity and biochemical data at baseline that could be used in multivariable models to adjust for the effect of confounders. The statistical analysis was extensive and involved assessment of the time-bias, a factor that can easily confound the association between nutritional intake and outcome.

On the other hand, the range of DCI was small, thus, despite being the largest study to date, we may have insufficient power to detect an independent association due to the limited number of patients with a DCI >25 Kcal/Kg/day. We could not account for unrecorded variables (such as gastrointestinal dysfunction) that may have affected DCI. We do not have information to explain why caloric intake was low and why it took an average of approximately 4 days for nutrition to reach a plateau. Moreover, data were only available from the time of randomization and did not provide information on mean DCI prior to treatment or after 28 days or ICU discharge. However, the fact that in the RENAL trial the time between ICU admission and randomization was <2 days and the mean duration of study time was approximately 13 days all suggest that the pre-randomization period was unlikely to materially affect the study findings. In addition, the sensitivity analysis showing that the 28-day outcome assessment leads to the same findings as the 90-day outcome assessment provides evidence that interventions after day 28 or ICU discharge are unlikely to have influenced our observations. We did not collect information on the daily dose of propofol infusion. Thus, we cannot quantify its caloric contribution. We do not have information on insulin intake and glucose control. However, glucose management in ANZ has remained steady over the last decade with a mean glucose value of approximately 8 mmol/L [34]. We do not have information on the caloric input derived from normal oral intake. However, such intake was uncommon in these critically ill patients while in ICU and is difficult to quantify. We consider that its overall contribution was negligible. Finally, we do not report on the calories delivered to patients by means of CRRT because its estimate is problematic. All CRRT was performed in all patients with bicarbonate fluids containing 1 g of glucose per liter (5.55 mmol/L) thus potentially delivering 200 to 300 Kcal/day. However, half of the fluid was administered as dialysate, where glucose movement into the patient's blood stream would be dependent on the glucose gradient and dynamically influenced by the patient's glucose level. Thus, in hyperglycemic patients, CRRT may have resulted in glucose and caloric loss in hyperglycemic patients and in caloric gain in normoglycemic patients. Such losses and gains would have varied over time according to glycemia, filter function, down time and CRRT intensity making correct estimates essentially impossible.

Conclusions

In the RENAL study, overall mean DCI was low. However, patients with a lower mean DCI had similar mortality than those with a higher DCI and non-survivors had a similar mean DCI to survivors. After correction for multiple confounding variables and the application of different statistical modeling techniques, a lower mean DCI was not robustly independently associated with increased risk of death at 90 days, or with other major clinical outcomes. Higher-level evidence is needed to better define the optimal DCI target in this important subgroup of patients.

Key messages

- In the largest multicenter study of AKI treatment with CRRT to date, the average mean DCI was low at 11 KCal/Kg/day
- In severe AKI patients stable calorie intake was only achieved at 4 to 5 days after randomization
- Patients with a low or high mean DCI had similar mortality rates
- Mean DCI was similar among survivors and non-survivors
- After adjustment for multiple confounders, increased daily DCI during study treatment was not independently associated with decreased mortality, decreased RRT-free days ICU-free days or hospital-free days

Additional files

Additional file 1: Names of ethical bodies that approved the study. This file contains information on all institutional review boards that have approved the study.

Additional file 2: Table S1. Multivariate logistic regression model for day-90 mortality including only patients who survived >96 hrs. **Table S2** Multivariate linear regression of renal replacement therapy (RRT)-free days including only patients who survived >96 hrs. **Table S3** Multivariate linear regression of mechanical ventilation-free days including only patients who survived >96 hrs. **Table S4** Multivariate linear regression of ICU-free days including only patients who survived >96 hrs. **Table S5** Multivariate linear regression of hospital-free days including only patients who survived >96 hrs. **Table S6** Cox regression model for death at day 90.

Abbreviations

AKI: acute kidney injury; ANZ: Australia and New Zealand; APACHE: acute physiology and chronic health evaluation; APPT: activated partial thromboplastin time; CRRT: continuous renal replacement therapy; CVVHDF: continuous veno-venous hemodiafiltration; DCI: daily calorie intake; FiO2: inspired oxygen fraction; IHD: intermittent hemodialysis; INR: international normalized ratio; OR: odds ratio; PaCO2: tension of carbon

dioxide in arterial blood; PaO2: arterial partial pressure of oxygen; RCT: randomized controlled trial; RENAL: Randomized evaluation of normal vs. augmented level of replacement therapy study; RRT: renal replacement therapy; SOFA: sequential organ failure assessment.

Competing interests

Professor Rinaldo Bellomo reports having received consulting fees as advisor for Gambro.

No other potential conflict of interest relevant to this article was reported.

Authors' contributions

RB: conception and design, obtaining of funding to conduct the study; supervision of analysis and interpretation of data; drafting of the manuscript and revising it critically for important intellectual content; writing and final approval of manuscript. AC: conception and design, analysis and interpretation of data; drafting of the manuscript and revising it critically for important intellectual content; obtaining of funding to conduct the study; writing and final approval of manuscript. LC: conception and design, analysis and interpretation of data; drafting of the manuscript and revising it critically for important intellectual content; obtaining of funding to conduct the study; writing and final approval of manuscript. SF: conception and design, analysis and interpretation of data; obtaining of funding to conduct the study, drafting of the manuscript and revising it critically for important intellectual content; writing and final approval of manuscript. MG: conception and design, analysis and interpretation of data; obtaining of funding to conduct the study, drafting of the manuscript and revising it critically for important intellectual content; writing and final approval of manuscript. CM: conception and design, analysis and interpretation of data; obtaining of funding to conduct the study, drafting of the manuscript and revising it critically for important intellectual content; writing and final approval of manuscript. SM: conception and design, analysis and interpretation of data; obtaining of funding to conduct the study, drafting of the manuscript and revising it critically for important intellectual content; writing and final approval of manuscript. JM: conception and design, analysis and interpretation of data; obtaining of funding to conduct the study, drafting of the manuscript and revising it critically for important intellectual content; writing and final approval of manuscript. RN: conception and design, analysis and interpretation of data; obtaining of funding to conduct the study, drafting of the manuscript and revising it critically for important intellectual content; writing and final approval of manuscript. CS: conception and design, analysis and interpretation of data; obtaining of funding to conduct the study, drafting of the manuscript and revising it critically for important intellectual content; writing and final approval of manuscript. JL: acquisition of data, analysis and interpretation of data; drafting of the manuscript and revising it critically for important intellectual content; supervision; writing and final approval of manuscript. SL: acquisition of data, statistical analysis, analysis and interpretation of data; drafting of the manuscript and revising it critically for important intellectual content; writing and final approval of manuscript. All authors meet key authorship requirements and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors read and approved the final manuscript.

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Chapter 11

Daily Protein Intake and Patient Outcomes in Severe Acute Kidney Injury: Findings of the Randomized Evaluation of Normal versus Augmented Level of Replacement Therapy (RENAL) Trial

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Daily Protein Intake and Patient Outcomes in Severe Acute Kidney Injury: Findings of the Randomized Evaluation of Normal versus Augmented Level of Replacement Therapy (RENAL) Trial

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Key Words
Protein intake · Acute kidney injury · Hemofiltration · Nitrogen balance · Nutrition

Abstract

Background and Aims: We aimed to examine the association between daily protein intake (DPI) and outcomes in patients from the Randomized Evaluation of Normal versus Augmented Level (RENAL) trial. ***Methods:*** We analyzed the association between DPI and clinical outcomes using multivariable logistic regression, Cox proportional hazards models and time-adjusted analysis. ***Results:*** During ICU stay, mean DPI was 37.6 g/day among survivors and 37.7 g/day among nonsurvivors (p = 0.96; DPI of 0.5 g/kg/day). Only 159 (10.9%) of the patients received a mean DPI of >1 g/kg. Patients with a DPI above the median had a 43.1% mortality compared with 46.1% for a DPI below the median (p = 0.25). On multivariate analysis, a lower DPI was not associated with increased odds ratios for 90-day mortality or any secondary outcomes. Cox proportional hazards models and time-adjusted analysis confirmed these findings. ***Conclusions:*** In the RENAL study, mean DPI was low. Within the confines of such low DPI, greater amounts of DPI were not independently associated with improved clinical outcomes.

Video Journal Club "Cappuccino with Claudio Ronco" at http://www.karger.com/?doi=363175.

Introduction

Achieving an adequate daily protein intake (DPI) is widely considered beneficial in critically ill patients in general and in patients with acute kidney injury (AKI) in par-

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ticular [1–3]. Accordingly, in these patients, nutritional guidelines recommend consideration of intravenous parenteral amino acids and the early administration of enteral nutrition whenever possible, targeted to achieve a protein intake of at least >1 g/kg/day and preferably >1.5 g/kg/day [4–6].

Unfortunately, all studies of protein intake in AKI conducted so far have been small and single center [7–13]. Thus, there are no large multicenter observational studies to (a) describe current practice and (b) assess whether protein intake in patients receiving renal replacement therapy (RRT) carries an independent association with patient-centered outcomes.

This lack of knowledge is problematic because protein intake may be a determinant of outcome and is modifiable. Moreover, critically ill patients with AKI receiving RRT represent close to 5% of all ICU patients and are typically some of the most acutely ill patients treated in ICU [14]. Such patients may represent a testing ground for the association between protein intake and outcome in the most critically ill patients in general.

The Randomized Evaluation of Normal versus Augmented Level (RENAL) study [15–19] is the largest randomized study of AKI treatment to date. It offers a unique opportunity to explore the independent association between DPI and outcome. Thus, we conducted a secondary analysis of the RENAL study findings focusing upon the relationship between DPI and primary and secondary clinical outcomes. We hypothesized that greater DPI would be independently associated with improved clinical outcomes.

Methods

The RENAL study was a multicenter, prospective, randomized trial of two levels of intensity of continuous RRT (CRRT) in 1,508 critically ill patients with AKI conducted in 35 ICUs in Australia and New Zealand (ANZ) [15] (ClinicalTrials.gov No.: NCT00221013). The Human Research Ethics Committees of the University of Sydney and all participating institutions approved the study.

The methodological details of the RENAL study were recently reported [19]. In brief, patients were eligible for enrollment if they were critically ill adults who had AKI, were deemed to require RRT by the treating clinician and fulfilled predefined criteria. Eligible patients were randomly assigned to continuous venovenous hemodiafiltration with effluent flow at 40 ml/kg/h (higher intensity) or 25 ml/kg/h (lower intensity). Study treatment was discontinued on death, discharge from ICU, or recovery of renal function. The primary study end point was death from any cause by day 90.

Daily Protein Intake

In all patients, DPI was calculated as the sum of all protein administered either by parenteral route, enteral route or both on each study day. Such data were prospectively collected as part of a standardized case report form.

We divided patients into two groups according to their mean DPI. A 'low' DPI was considered present when individual mean DPI was below the median value for the study population and a 'high' DPI was considered present when individual mean DPI was above the median value for the study population.

According to study protocol, DPI data were obtained until the first occurrence of either death, or ICU discharge or the completion of 28 days from study randomization (study treatment time).

Statistical Analysis

Continuous variables were expressed as means with standard deviation for normally distributed variables and as median and interquartile range for nonnormally distributed variables. Comparisons were made using Student's t test or the Mann-Whitney test where appropriate. Categorical variables were expressed as proportions and compared with the χ^2 test or Fisher's exact test as appropriate.

Patients with low and high mean DPI were first compared by univariate analysis. Mean DPI was calculated and DPI-related variables and treatment group, APACHE (acute physiology and chronic health evaluation) III diagnostic groups, daily use of CRRT, allocation to high- versus low-dose CRRT, study center, age, daily calorie intake, time from ICU to randomization, presence of sepsis, Sequential Organ Failure Assessment (SOFA) respiratory score, SOFA coagulation score, SOFA liver score, SOFA cardiovascular score, SOFA renal score, presence of nonrenal organ failure, international normalized ratio for prothrombin time, activated partial thromboplastin time, platelet count, serum creatinine, PaO_2/FiO_2 ratio, $PaCO_2$, use of mechanical ventilation, mean daily fluid balance, clinical diagnosis of significant edema at randomization, and all other variables with a significant difference on univariate comparison were used to create backwards elimination multivariable models with a 5% threshold using survival to 90 days as the dependent variable. The models were tested for collinearity and were found to have a low variance inflation factor.

Multivariable linear regression analysis was used to assess the relationship between mean DPI and mechanical ventilation-free days, RRT-free days and ICU-free days at 90-day follow-up as the dependent variables. Analysis of time to death within 90 days of randomization used the Kaplan-Meier product limit estimates and compared survival curves using the log-rank test. Because data collection was censored at 28 days, we additionally assessed the relationship between DPI and 28-day mortality and because a DPI >1 g/kg/day is generally recommended, we also assessed the relationship between a DPI >1 g/kg/day and 28-day mortality.

To test the robustness of any association between mortality and DPI, we then applied Cox proportional hazards modeling with adjustment for the above variables and pattern analysis to assess whether pattern mixture modeling could be applied. As an additional analysis, we performed multivariable regression analysis for 90-day mortality after excluding patients who had died before 96 h. This choice was based on the finding that DPI appeared to plateau after day 4 and that early DPI was much lower. This difference created an artificial mortality bias against low DPI, because the achievement of full nutritional support was time-dependent and patients who died in the first few days were

Table 1. Key baseline characteristics and major outcomes of patients with a low (below median) versus high (above median) DPI

Baseline characteristics	Low DPI (n = 727)	High DPI (n = 730)	p
Age	65.8±14.5	63.3±15.1	0.0012
Male sex	455/727 (62.6%)	486/730 (66.6%)	0.114
Weight	79.8±12.8	81.5±13.0	0.0142
Mechanical ventilation	432/727 (59.4%)	644/730 (88.2%)	<0.0001
Time from ICU admission to randomization, h	27.2±52.9	75.9±156	<0.0001
Source of admission to ICU			
Accident and emergency department	185/687 (26.9%)	163/678 (24.0%)	0.0277
Hospital floor/ward	212/687 (30.9%)	175/678 (25.8%)	
Transfer from another ICU	49/687 (7.1%)	60/678 (8.8%)	
Transfer from another hospital, except from ICU	70/687 (10.2%)	84/678 (12.4%)	
Admitted from operating room/recovery following emergency surgery	86/687 (12.5%)	118/678 (17.4%)	
Admitted from operating room/recovery following elective surgery	85/687 (12.4%)	78/678 (11.5%)	
Nonoperative admission diagnosis			
Cardiovascular	252/539 (46.8%)	280/507 (55.2%)	<0.0001
Genitourinary	177/539 (32.8%)	52/507 (10.3%)	
Gastrointestinal	36/539 (6.7%)	39/507 (7.7%)	
Hematology	8/539 (1.5%)	14/507 (2.8%)	
Metabolic/endocrine	14/539 (2.6%)	11/507 (2.2%)	
Neurologic	4/539 (0.7%)	6/507 (1.2%)	
Respiratory	44/539 (8.2%)	102/507 (20.1%)	
Transplant	4/539 (0.7%)	1/507 (0.2%)	
Trauma	0/539 (0.0%)	2/507 (0.4%)	
Severe sepsis at baseline	302/727 (41.5%)	417/730 (57.1%)	<0.0001
APACHE III score	104.0±25.8	100.9±25.5	0.018
SOFA respiration score	2.5±1.1	3.0±0.7	<0.0001
SOFA coagulation score	0.8±1.0	1.1±1.2	<0.0001
SOFA cardiovascular score	2.7±1.6	3.0±1.4	<0.0001
SOFA renal score	2.9±1.1	2.6±1.0	<0.0001
Last creatinine concentration, μmol/l	369.7±228	299.7±147	<0.0001
Bicarbonate, mmol/l	17.1±5.7	19.5±5.7	<0.0001
Creatinine, μmol/l	374.0±248	298.9±151	<0.0001
pH	7.2±0.1	7.3±0.1	<0.0001
Base excess, mEq/l	−9.8±6.8	−6.8±6.8	<0.0001
eGFR	52.3±30.9	60.8±30.5	<0.0001

Continuous variables are expressed as means ± SD and nominal variables as numbers with percentages in parentheses. MV = Mechanical ventilation; eGFR = estimated glomerular filtration rate.

more likely to receive a low DPI thus creating an artificial association between lower DPI and mortality. We further tested for this effect by performing a time-dependent Cox proportional hazards model with or without exclusion of patients who died in the first 96 h.

A two-sided $p < 0.05$ was taken to indicate statistical significance. Statistical analyses were performed and independently checked with the use of SAS software, version 9.1.

Results

Of 1,508 patients enrolled in the RENAL study, complete DPI data were available for 1,457 (96.6%). The characteristics of these patients divided according to a mean DPI above (high) or below (low) the median DPI for the entire cohort are presented in table 1. In the overall cohort, mean daily caloric intake was 867 kcal/day, with a

Table 2. DPI according to survival status at 90 days after randomization

Baseline characteristics	All patients (n = 1,464)	Nonsurvivors (n = 654)	Survivors (n = 810)	p
DPI during time in ICU				
Patients, n	1,456	649	807	0.9673
Mean ± SD, g/day	37.7±33.3	37.7±35.0	37.6±32.0	
Q1/Q2/Q3, g/day	3.7/36.4/59.7	5.0/34.6/58.7	2.4/37.3/60.3	
Missing, n	8	5	3	
Weight-adjusted DPI during time in ICU				
Patients, n	1,456	649	807	0.5251
Mean ± SD, g/kg/day	0.5±0.4	0.5±0.5	0.5±0.4	
Q1/Q2/Q3, g/kg/day	0.1/0.5/0.7	0.1/0.4/0.7	0.0/0.5/0.7	
Missing, n	8	5	3	
Patients with a weight-adjusted mean DPI >1 g/kg/day				
No	1,297/1,456 (89.1%)	573/649 (88.3%)	724/807 (89.7%)	
Yes	159/1,456 (10.9%)	76/649 (11.7%)	83/807 (10.3%)	

Table 3. Multivariate logistic regression for 'death at day 90'

Variable name	Effect (discrete variable)	OR	95% CI	p
Median DPI during ICU admission	high vs. low	1.103	0.58–2.11	0.7673
Mean DPI during ICU admission		0.998	0.99–1.01	0.6413
Mean fluid balance, input-output (liters)		2.016	1.61–2.53	<0.0001
Median daily calorie intake during ICU admission	high vs. low	1.079	0.55–2.13	0.8275
Mean daily calorie intake during ICU admission		1.000	1.00–1.00	0.0636
Patient age		1.037	1.03–1.05	<0.0001
Patient weight (kg)		0.989	0.98–1.00	0.0394
Time from ICU admission to randomization (days)		1.002	1.00–1.00	0.0047
SOFA liver score	failure vs. normal	3.384	1.55–7.38	0.0022
INR		1.200	1.03–1.39	0.0172
Hemoglobin (g/l)		0.992	0.98–1.00	0.0353
Albumin (g/l)		0.977	0.96–1.00	0.0300
$PaCO_2$ (mm Hg)		1.016	1.00–1.03	0.0249

Only protein intake and calorie intake variables and variables with $p < 0.05$ are presented. INR = International normalized ratio for prothrombin time.

value of 883 kcal/day among survivors versus 847 kcal/day among nonsurvivors (p = 0.3185).

Among patients with a low mean DPI, 335 (46.1%) had died 90 days after randomization, compared with 314 (43.1%) patients with a higher mean DPI (p = 0.24). In addition, survivors and nonsurvivors had a similar DPI (table 2). During treatment, mean DPI among survivors was 37.6 versus 37.7 g/kg/day among nonsurvivors (p = 0.96) for a weight-adjusted mean DPI of 0.5 g/kg/day for both groups. Only 159 (10.9%) patients received a mean DPI of >1 g/kg on only 26.8% of study days. Overall, 382 patients received only parenteral nutrition for a total of 1,667 (13.8%) study days, and 200 patients received a combination of enteral and parenteral nutrition for a total of 2,055 (17.1%) study days. The daily DPI for survivors and nonsurvivors for the first 14 days of observation is compared in figure 1. DPI was similar in both groups and increased over time in both, reaching a plateau by day 4.

On multivariable logistic regression analysis, several variables were independently associated with 90-day

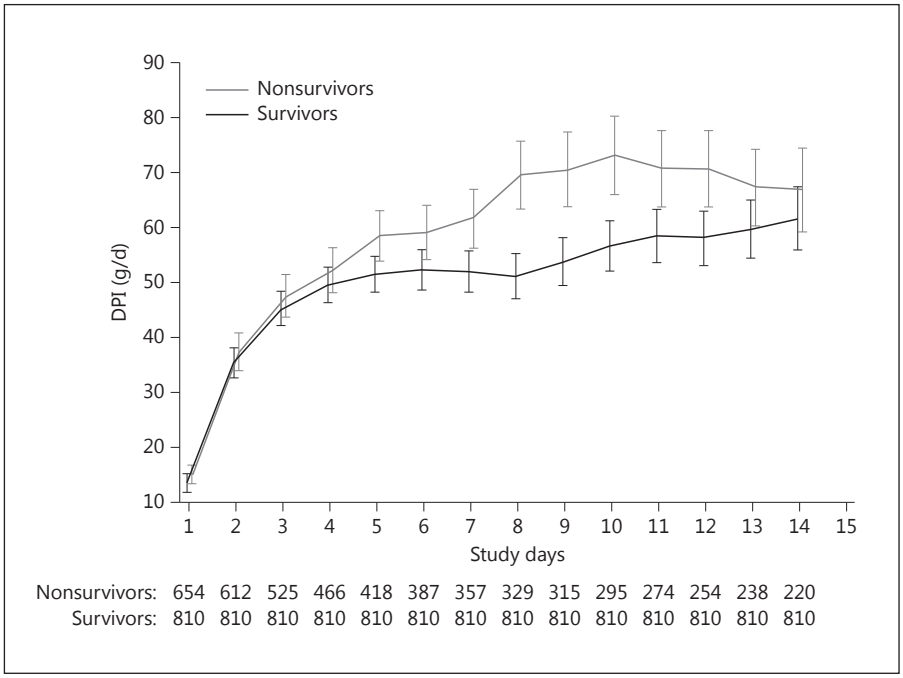

Fig. 1. Graphic representation of mean DPI (and 95% CI) over the first 2 weeks of observation after randomization according to survival status at 90 days. As can be seen, survivors had a lower DPI than nonsurvivors from day 7 to day 12.

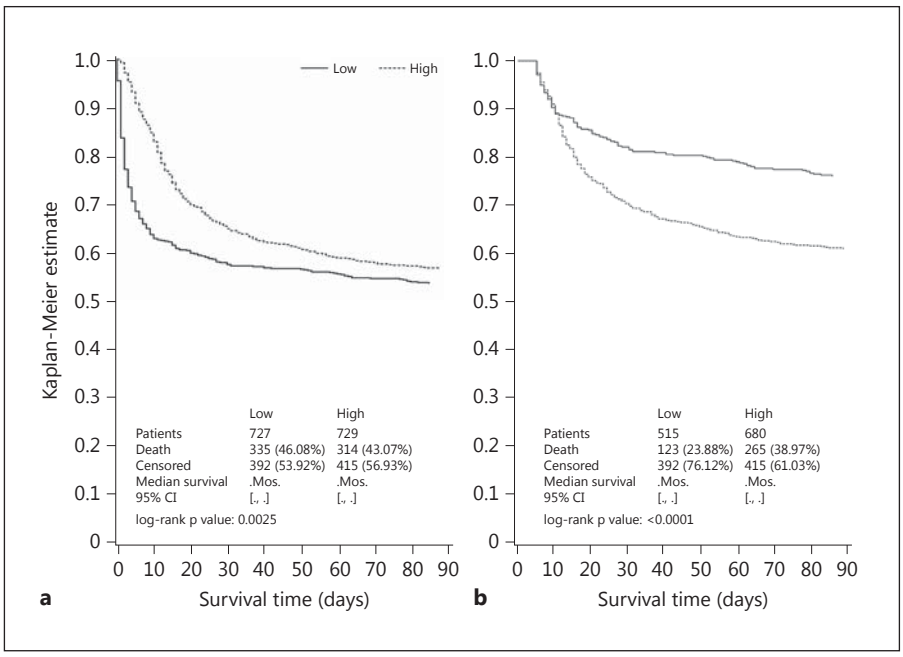

Fig. 2. a Kaplan-Meier graph of survival plots from randomization to day 90 stratified by the presence or absence of lower (below median) or higher (above median) DPI during the index ICU admission. **b** Kaplan-Meier graph of survival plots from randomization to day 90 among patients who survived >96 h stratified by the presence or absence of lower (below median) or higher (above median) DPI during the index ICU admission.

mortality (table 3) but mean daily DPI was not. When analysis was performed with 28-day mortality as the outcome, a DPI above the median carried an odds ratio (OR) of 0.98 (95% confidence interval, CI, 0.62–1.57; p = 0.95) and mean DPI carried an OR of 0.99 (95% CI 0.98–1.0; p = 0.15). Finally a DPI >1 g/kg/day had an OR for mortality of 0.63 (95% CI 0.36–1.13; p = 0.12). Time to event comparison using the log-rank test showed a significant difference in survival time in favor of patients with high mean DPI (fig. 2a). However, this effect was reversed once patients who died in the first 96 h were removed (fig. 2b).

Table 4. Multivariable linear regression models

Variable name	Estimates	SE	p
Multivariable linear regression model for RRT-free days			
Intercept	−40.32510	33.71933	0.2323
Mean DPI during ICU admission	**−0.01391**	**0.02507**	**0.5792**
Median DPI during ICU admission (high vs. low)	**0.99929**	**2.52307**	**0.6922**
Positive mean fluid balance	−4.09805	0.87492	<0.0001
Treatment intensity	−1.97170	0.85163	0.0210
Time from ICU admission to randomization (days)	−0.01644	0.00469	0.0005
SOFA liver score	−1.63540	0.44579	0.0003
APPT	−0.05581	0.02105	0.0083
pH	8.45062	4.27094	0.0484
Multivariable linear regression model for MV-free days			
Intercept	−23.71739	285.96733	0.9339
Mean DPI during ICU admission	**−0.02881**	**0.09283**	**0.7564**
Median DPI during ICU admission	**−3.16299**	**8.92563**	**0.7232**
Positive mean fluid balance	−19.28802	3.41162	<0.0001
Positive ventilation: no as reference group	−14.91985	5.71577	0.0094
Patient weight (kg)	0.53574	0.14153	0.0002
Last creatinine concentration	0.10963	0.04656	0.0190
Multivariable linear regression model for ICU-free days			
Intercept	−221.76773	281.51940	0.4313
Mean DPI during ICU admission	0.03687	0.08936	0.6801
Median DPI during ICU admission	−5.83877	8.44694	0.4898
Positive mean fluid balance	−19.69578	3.36383	<0.0001
Positive ventilation: no as reference group	−13.45268	5.58339	0.0165
Patient weight (kg)	0.45320	0.13896	0.0012
Time from ICU admission to randomization (days)	−0.03736	0.01756	0.0340
Last creatinine concentration	0.11279	0.04434	0.0114
Multivariable linear regression model for hospital-free days			
Intercept	25.05875	258.6057	0.9229
Mean DPI during ICU admission	−0.04355	0.08277	0.5991
Median DPI during ICU admission	0.80365	7.90876	0.9191
Positive mean fluid balance	−16.17529	3.08521	<0.0001
Patient weight (kg)	0.29499	0.12933	0.0231
Last serum urea concentration	−3.72244	1.85441	0.0454
Last creatinine concentration	0.09767	0.04131	0.0185
Glucose (mmol/l)	1.09456	0.50830	0.0319

SE = Standard error; APTT = activate partial thromboplastin time. Only DPI data and variables with a $p < 0.05$ are displayed.

Most of the death occurred in the low group within the first 96 h (212 deaths in the low group vs. 49 deaths in the high group). In this analysis, 341 patients did not receive any protein intake. Of all the 727 patients receiving a low (<median) protein intake, 335 (46.1%) died compared with 314 (43.15) of 729 patients among those receiving high (>median) protein intake. When patients who survived the first 96 h (time when DPI appeared to stabilize) were considered, 123 (23.9%) of 515 low DPI patients died compared with 265 (40%) of 415 patients receiving a high DPI ($p < 0.0001$).

Cox proportional hazards modeling failed to detect an independent association between DPI and 90-day mortality. Time-dependent Cox proportional hazards model

confirmed the findings of other models. Pattern analysis found that pattern mixture modeling could not be applied.

On multivariable linear regression analysis, mean DPI showed no association with decreased RRT-free days at day 90 after randomization, mechanical ventilation-free days, ICU-free days or hospital-free days (table 4). This lack of association with mortality and morbidity was confirmed when time-adjusted analysis was applied assessing the 1,183 patients who were alive after 96 h.

Discussion

Statement of Key Findings

Using data from a large, multicenter, randomized, controlled trial of the intensity of CRRT in critically ill patients with AKI, we assessed the association between mean DPI and clinically important outcomes. We found that DPI was generally low with a mean value of 0.5 g/kg/day and that only 10% of patients averaged a DPI of >1 g/kg/day. Within the confines of such a low DPI, patients with a DPI above or below the median had a similar mortality, and nonsurvivors had a similar DPI to survivors. In addition, DPI was not independently associated with decreased OR for mortality, or increased RRT-free days, mechanical ventilation-free days, ICU-free days and hospital-free days. Although unadjusted time to death analysis initially showed a favorable unadjusted association with DPI, this finding was biased by the time-dependent nature of DPI. Once the impact of such time-dependent effect was attenuated by time-adjusted analysis, this relationship was reversed. Moreover, Cox proportional hazards modeling confirmed the findings of the multivariable models. Finally, when patients who survived >96 h (the time when DPI stabilized) were analyzed separately, those receiving a higher DPI had a significantly greater mortality rate.

Comparison with Previous Studies

There are no epidemiological studies of current protein delivery practice in patients with AKI. In general critically ill patients, a recent multicenter observational found that mean DPI was 0.6 g/kg/day [20], a value similar to our study. Thus, current protein administration practice in ANZ appears to be similar to current ICU practice worldwide.

Authors [2, 3] and guidelines [1, 6] continue to recommend a protein intake of at least >1 g/kg/day in AKI patients, but the evidence supporting such recommendations is weak [7–13]. Moreover, although such recommendations appear reasonable from a nitrogen-balance point of view, especially given the loss of amino acids during CRRT [21–27], the only randomized controlled trial focusing on clinical outcomes was conducted in 1973 [28] and has little relevance to modern practice. Moreover, recent investigations have suggested that permissive underfeeding, trophic feeding, or delayed parenteral feeding may be equivalent or perhaps superior to currently recommended approaches [29–32].

Significance of Study Findings

Our findings expand our understanding of current practice and the relationship between DPI and outcome in severe AKI in the setting of essentially exclusive CRRT use. This aspect is important because during CRRT, volume control and full nutritional therapy are always possible [32]. Thus, DPI in this setting can be logically taken to reflect therapeutic choices rather than technical limitations [33, 34].

Our study demonstrates that current practice in ANZ delivers a low DPI, well below current guidelines, in the overwhelming majority of patients with severe AKI. This disconnect from published guidelines remains unexplained. Given that practice in ANZ ICUs is likely similar to other developed countries, it appears that low DPI in AKI patients may be common.

A low DPI is likely to be associated with a strongly negative nitrogen balance [33], and a negative nitrogen balance may be associated with increased mortality [34]. Our assessment, however, failed to provide evidence of an independent association between greater DPI and favorable outcome. Recent data suggest that more protein intake may inhibit autophagy and delay recovery in critically ill patients [35]. Moreover, studies of supplemental [36] and early parenteral nutrition [37] have delivered contradictory findings. Thus, it is not surprising that our understanding of optimal protein intake in renal disease, which is limited in patients with chronic kidney disease [38], in those on chronic dialysis [39], and in patients receiving continuous or intermittent extended RRT [40–42] generates great variability in feeding practices in ICU [20, 43].

A lack of association was seen despite the presence of a bias in favor of a high DPI. For example, patients who died in the first 2–3 days after randomization were most likely to receive little DPI because full nutritional therapy was typically achieved over time (about 4 days on average). Thus, those patients who achieved higher DPIs were essentially the same patients who had survived long

enough to achieve the higher rates of DPI delivered later in the course of ICU stay. However, sicker patients may have received endotracheal intubation for longer and nasogastric feeding at full dose for longer, while patients receiving early extubation may have also received less nasogastric feeding. These confounding and complex selection biases cannot be corrected by statistical techniques.

Study Strengths and Limitations

This study reports observational findings from the largest randomized controlled study of CRRT for AKI to date. The data were detailed and prospectively collected with specific attention to DPI and independently monitored for accuracy. As such, they provide the most comprehensive description of DPI during CRRT and of its association with outcomes to date.

On the other hand, we did not provide information on DPI prior to or after treatment. However, the time between ICU admission and randomization was <2 days, and the mean duration of study time was approximately 13 days, suggesting that the prerandomization period was unlikely to materially affect the study findings. In addition, it seems unlikely that DPI following ICU discharge would have biased our findings. In this regard, sensitivity analysis focusing on 28-day outcome was consistent with our primary 90-day mortality analysis. The use of high-dose CRRT might have led to greater protein loss and thus influenced the relationship between DPI and outcome. However, dose of CRRT was taken into account in multivariable models and showed no interaction with the relationship between DPI and outcome. We could not account for oral intake. However, such intake was uncommon in these patients while in ICU, and only nasogastric feeding nutritional data were recorded. Finally, we chose the mean dose of DPI as the metric for nutritional assessment. Other metrics (maximum daily dose or number of days above a given percentage of prescribed nutrition) could be used to analyze protein therapy in our study patients. However, it is unlikely that such metrics would materially alter our findings.

Conclusions

In the RENAL study, patients received a low DPI, markedly below current recommendations. Within the confines of such DPI, patients with a low DPI had similar mortality to those with a high DPI, and nonsurvivors had a similar DPI to survivors. After correction for multiple confounding variables and the application of different statistical modeling techniques, a low DPI was not independently associated with a decreased risk of death at 90 days or an increase in mechanical ventilation, RRT, ICU and hospital-free days.

Acknowledgement

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Disclosure Statement

Prof. Rinaldo Bellomo reports having received consulting fees as advisor for Gambro. There is no other potential conflict of interest relevant to this article.

Appendix

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Chapter 12

Angiotensin-converting enzyme inhibitor usage and acute kidney injury: A secondary analysis of RENAL study outcomes

NEPHROLOGY

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Original Article

Angiotensin-converting enzyme inhibitor usage and acute kidney injury: A secondary analysis of RENAL study outcomes

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KEY WORDS:
acute kidney injury, angiotensin-converting enzyme inhibitor, dialysis, mortality, prospective study.

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SUMMARY AT A GLANCE

In this RENAL study cohort, the use of ACEI in AKI during the study was not common and was not significantly associated with reductions in mortality.

ABSTRACT:

Aim: **Acute kidney injury (AKI) is associated with increased mortality. While angiotensin-converting enzyme inhibitors (ACEI) are known to slow progression of chronic kidney disease, their role in AKI remains unclear.**

Methods: **The Randomised Evaluation of Normal vs. Augmented Level Replacement Therapy (RENAL) study data were analysed according to ACEI use over time. The primary outcome was all-cause mortality at 90 days following randomisation. Analyses used a multivariate Cox model adjusted for either baseline or for time-dependent covariates, and a sensitivity analysis of patients surviving to at least the median time to ACEI initiation.**

Results: **Of the 1463 participants with available data on ACE inhibitors usage, 142 (9.7%) received ACEI at least once during study data collection. Participants treated with ACEI were older ($P = 0.02$) and had less sepsis at baseline ($P < 0.001$). ACEI use was significantly associated with lower mortality at 90 days (HR 0.46, 95% CI 0.30-0.71, $P < 0.001$), and an increase in renal replacement therapy-free days ($P < 0.001$), intensive care unit-free days ($P < 0.001$) and hospital free-days ($P < 0.001$) after adjusting for baseline covariates. Using the time-dependent analysis, however, the effect of ACEI administration was not significant (HR 0.78, 95% CI 0.51-1.21, $P = 0.3$). The sensitivity analysis in day 8 survivors produced similar results.**

Conclusion: **In the RENAL study cohort, the use of ACEI during the study was not common and, after adjustment for time-dependent covariates, was not significantly associated with reductions in mortality. Further assessment of the effect of ACEI use in AKI patients is needed.**

*The Randomised Evaluation of Normal vs. Augmented Level (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 Global Health.

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Acute kidney injury (AKI) is estimated to be some ten times more common than end-stage kidney disease[1] and is associated with a mortality rate of up to 60%[2] and prolongation of hospitalization.[1,3] AKI is particularly common in patients admitted to intensive care units (ICU),[4] with up to 20% of critically ill patients experience an episode of AKI during the course of their admissions.[4]

There has been increasing recognition of the renoprotective effect of angiotensin-converting enzyme inhibitors (ACEI) in chronic kidney disease (CKD),[5] with a number of guidelines recommending their use to reduce proteinuria and slow progression of CKD.[6–10] However, their role in AKI remains uncertain, particularly in the intensive care setting, where exposure to ACEI could potentially exacerbate AKI through vasodilatation of the efferent arteriole and resultant reduction in glomerular filtration pressure.[11] Currently, there is a paucity of literature to assess the association of ACEI use with clinical outcomes in AKI.

The Randomised Evaluation of Normal vs. Augmented Level (RENAL) study assessed the effect of two different dialysis dose intensities upon patients with AKI in ICU and showed no difference in mortality at 90 days.[12] Using prospectively collected data on baseline and daily use of ACEI, we conducted a secondary analysis to explore the effect of ACEI usage upon clinical outcomes.

MATERIALS AND METHODS

The RENAL study was a multicentre, randomised controlled trial of intensity of continuous renal replacement therapy (RRT) in 1508 critically ill patients with AKI.[12] The details of the study were reported elsewhere.[12] In brief, eligible patients were in ICU with AKI and deemed to require RRT by the treating clinician on the basis of having at least one of five criteria. Patients were randomly assigned to continuous veno-venous haemodiafiltration with effluent flow at 40 mL/kg per hour (higher intensity) or 25 mL/kg per hour (lower intensity). The primary study outcome was all-cause mortality by day 90.

Use of ACEI

Data on the use of ACEI were collected at study baseline and daily on each study day after randomisation until the first occurrence of death, ICU discharge, or completion of 28 days from study randomisation. Use of ACEI was documented as binary data (yes or no) during the ICU admission and did not include the dose or name of the agent.

Study outcomes

The primary outcome of this analysis was all-cause mortality at 90 days following randomisation. The secondary outcomes were 28 day mortality (death within 28days after randomisation), RRT-free days (defined as the number of days between the cessation of RRT and the 90 day follow-up), ICU-free days (defined as the number of days from ICU discharge to the 90 day follow-up), and hospital-free days (defined as the number of days from hospital discharge to the 90 day follow-up). ACEI use was defined as the recorded use of ACEI at any stage during study data collection.

Statistical analysis

Continuous variables were reported as means with standard deviation (SD) for normally distributed variables and as median and interquartile range (IQR) for non-normally distributed variables. Comparisons of means and medians were made using Student's *t*-test or the Mann–Whitney test when appropriate. Categorical variables were reported as proportions and the χ^2 test was conducted for comparison.

Baseline variables, including ACEI usage, were used to construct Cox proportional hazards models, using mortality at 90 days as a dependent variable. The selection of variables was based on identifying all measured clinical variables of known or suspected prognostic importance for the outcomes of interest. The baseline variables that were assessed included demographic (age and gender), biochemical (haemoglobin, potassium, albumin, bicarbonate), clinical (mechanical ventilation, sepsis at baseline, urine output and haemodialysis), and illness severity scores (Acute Physiology and Chronic Health Evaluation III (APACHEIII) score, Sequential Organ Failure Assessment (SOFA) cardiovascular score and mean SOFA score). A survival curve adjusted for covariates was estimated by the relevant Cox model to compare survival between the ACEI and non-ACEI groups. Multivariable analysis was then performed to assess the association of ACEI use with all-cause mortality at 90 and 28 days. The association of ACEI use and hospital free days, ICU free days as well as RRT-free days was analysed by adjusting for baseline variables.

In view of the potential for survivorship bias a sensitivity analysis was performed to examine the effect of use of ACEI on 90 day and 28 day mortality among patients who survived at least the median day of ACEI initiation after study randomisation.

Recognising that some clinical important variables may change in value over the study period, time-dependent variable analysis was employed. The time-dependent Cox analysis used the variables measured on a daily basis (daily urine output, severity of illness as assessed by mean sofa scores, sofa cardiovascular scores, metabolic acidosis (as assessed by serum bicarbonate), serum albumin, potassium and haemoglobin, and haemodialysis status) as time-dependent covariates in the model, along with non-time-dependent baseline variables.

A two-sided $P < 0.05$ was used to indicate statistical significance. Statistical analyses were performed with the use of SAS software version 9.3.

RESULTS

Patient characteristics at baseline

Of the 1508 patients enrolled in the RENAL study, complete information on ACEI use was available for 1463 participants (97.0%), with 142 participants (9.7%) administered ACEI at least once during study data collection. The average time of first use of ACEI after randomisation was 8 days and,

Table 1 Baseline characteristics of study participants by ACEI exposure

Variables	ACEI group (n = 142)	Non-ACEI group (n = 1321)	P-value
Age (years)	67.3 ± 14.3	64.2 ± 14.9	0.02
Male (%)	66.9%	64.4%	0.5
APACHEIII (points)	97.9 ± 22.4	102.9 ± 26.0	0.03
Severe sepsis at baseline (%)	34.5%	50.9%	0.0002
Mechanical ventilation (days)	11.1 ± 8.9	6.9 ± 7.2	<0.0001
Mean SOFA score (points)	2.0 ± 0.4	2.1 ± 0.6	0.6
Cardiovascular SOFA score (points)	3.2 ± 1.5	3.0 ± 1.7	0.2
Serum creatinine (μmol/L)	283.7 ± 132.7	308.9 ± 184.9	0.2
Haemodiaylsis (%)	0.07	0.14	0.2
Urine output (mL)	300.2 ± 360.0	422.6 ± 709.3	0.04
Serum potassium (mmol/L)	4.6 ± 0.7	4.6 ± 0.8	0.6
Serum bicarbonate (mmol/L)	19.5 ± 0.4.8	19.1 ± 5.6	0.4
Serum Albumin (g/L)	26.4 ± 6.2	25.8 ± 6.8	0.4
Haemoglobin (g/L)	100.3 ± 19.1	97.1 ± 17.5	0.08
Type of admission (%)			
Admit from ED	17.2	26.3	<0.0001
Admit from Hospital floor/ward	25.3	28.6	
Transferred from another ICU	2.0	8.8	
Transferred from another hospital	15.2	10.8	
Admit from OT following emergency operation	19.2	14.7	
Admit from OT following elective operation	21.2	10.9	

Values are represented as mean ± standard deviation or frequency. ACEI, angiotensin-converting enzyme inhibitor; APACHEIII, acute physiology and chronic health evaluation III; ED, emergency department; ICU, intensive care unit; OT, operation theatre; SOFA, sequential organ failure assessment.

after ICU admission, it was 9 days. The association of ACEI use with patient baseline characteristics and laboratory parameters are summarized in Table 1. Participants treated with ACEI were older than those not treated with ACEI (mean age of 67.4 and 64.2 respectively, $P = 0.02$), had lower disease severity as assessed by APACHE III score (97.9 and 102.9 respectively, $P = 0.03$), less sepsis at baseline (34.5% and 50.9% respectively, $P < 0.001$), longer duration for mechanical ventilation during the study (11.1 and 6.9 days, $P < 0.0001$) and lower urine output (300.2 *vs* 422.6 mL, $P = 0.04$). There were 420 participants (28.7%) admitted to ICU following surgical procedures. More participants underwent surgery in the ACEI group than in the non-ACEI group (43.0% *vs* 27.2%, $P < 0.0001$). There were 770 patients reported RRT-free days up to day 28. Among them, 75 patients (9.7%) died in the subsequent 29–90 days, while the majority of patients (90.3%) survived to day 90. Patients receiving ACEI had slightly longer duration of survival than those not on ACEI (85.9 *vs* 85.6 days). The majority of patients did recover and did not have support withdrawn.

Primary and secondary outcomes

Univariate Cox analysis showed that non-ACEI use, advanced age, higher APACHEIII score, SOFA cardiology and mean SOFA score, the presence of sepsis, use of ventilation, and lower urine output were associated with increased risk of all-cause mortality at 90 days. Kaplan–Meier survival plots from randomisation to day 90 showed lower mortality at day 90 in patients receiving ACEI ($\chi^2 = 26.53$, $P < 0.0001$) (Fig. S1).

In multivariate Cox proportional hazard models (Table 2 and Fig. 1), ACEI use was independently associated with a decreased mortality at 90 days (HR 0.46, 95% CI 0.30–0.71, $P < 0.001$) when adjusted for baseline variables. In addition, ACEI use was associated with lower mortality at 28 days (HR 0.38, 95% CI 0.23–0.63, $P < 0.001$) (Table S1) along with increases in RRT-free days ($P = 0.001$), ICU-free days ($P < 0.0001$) but not hospital free-days ($P = 0.4$).

Time-dependent analyses

As the indication for ACEI administration is affected by the clinical condition of the patients in a setting of acute illness, we adjusted for time-dependent covariates in both the entire study dataset and, in a sensitivity analysis, on the subset of patients who survived beyond the median day of ACE initiation (day 8 post randomisation). In the time-dependent analysis of the entire study dataset, ACEI administration was no longer a significant factor in mortality at both 90 days (HR 0.78, 95% CI 0.51–1.21, $P = 0.3$, Table 3) and 28 days (HR 0.80, 95% CI 0.52–1.24, $P = 0.3$, Table S3). After adjustment for surgical status at baseline, the effect of ACEI on mortality at day 90 remained non-significant (HR 0.80, 95% CI 0.51–1.23, $P = 0.3$).

The further sensitivity analysis of patients surviving at least 8 days included 1126 of 1463 (77.0%) RENAL study participants, 135 (12.0%) of whom received ACEI. Two (2.2%) patients in ACEI group and 49 (4.7%) patients in non-ACEI group were still on RRT by day 8. The mean creatinine for the ACEI and the non-ACEI groups were 215.3 ± 109.6 μmol/L and 195.1 ± 129.6 μmol/L, respectively. The mean urea for the ACEI and the non-ACEI groups were 16.1 ± 8.6 mmol/L and 13.4 ± 7.0 mmol/L, respectively. In this analysis, participants treated with ACEI were older than those not treated with ACEI (mean age of 67.7 and 63.4 respectively, $P = 0.002$), had less sepsis at baseline (35.6% and 49.1% respectively, $P = 0.003$), but similar disease severity as assessed by APACHEIII score (97.1 and 99.4 respectively, $P = 0.3$) (Table S2).

There was no survival benefit of ACEI administration at both 90 (HR 0.80, 95% CI 0.47–1.34, $P = 0.4$, Table 3) and 28 days (HR 0.82, 95% CI 0.49–1.38, $P = 0.5$, Table S3) among day 8 survivors after adjustment for time-dependent variables. This time-dependent model saw notable increases in the hazard ratios for both mean and cardiovascular SOFA scores compared with the non-time-dependent Cox model.

Table 2 Association of clinical parameters at baseline with the risk for 90 day mortality

Variables	Unit	Univariable model		Multivariable model†	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
ACEI administration	Yes *vs* No	0.42 (0.30–0.59)	<0.0001	0.46 (0.30–0.71)	0.0004
Age (years)	per 1 year older	1.01 (1.01–1.02)	<0.0001	1.11 (1.01–1.02)	<0.0001
Male (%)	Male *vs* women	1.04 (0.89–1.23)	0.7	1.07 (0.86–1.33)	0.5
APACHEIII	per 10 pts increment	1.15 (1.12–1.19)	<0.0001	1.08 (1.03–1.13)	0.007
Severe sepsis	Yes *vs* No	1.30 (1.12–1.52)	0.0008	1.02 (0.83–1.26)	0.8
Mechanical ventilation	Yes *vs* No	1.95 (1.58–2.41)	<0.0001	1.52 (1.10–2.10)	0.01
Mean SOFA	per 1 pts increment	1.67 (1.44–1.92)	<0.0001	1.27 (1.02–1.57)	0.03
Cardiovascular SOFA score	per 1 pts increment	1.19 (1.14–1.25)	<0.0001	1.07 (0.98–1.17)	0.1
Haemodialysis	Yes *vs* No	0.67 (0.09–4.72)	0.7	0.63 (0.09–4.53)	0.6
Urine output	per 100 mL increment	0.98 (0.97–1.00)	<0.0001	0.98 (0.97–1.00)	0.05
Serum potassium	per 0.5 mmol/L increment	1.05 (0.99–1.10)	0.09	1.07 (1.00–1.14)	0.06
Serum bicarbonate	per 5 mmol/L increment	0.97 (0.89–1.05)	0.5	1.00 (0.90–1.11)	0.9
Serum Albumin	per 10 g/L increment	0.80 (0.69–0.92)	0.002	0.88 (0.76–1.03)	0.1
Haemoglobin	per 10 g/L increment	0.97 (0.92–1.02)	0.3	0.97 (0.92–1.03)	0.4

†All variables listed were included in the model. ACEI, angiotensin-converting enzyme inhibitor; APACHEIII, acute physiology and chronic health evaluation III; CI, confidence interval; HR, hazard ratio; pts, points; SOFA, sequential organ failure assessment.

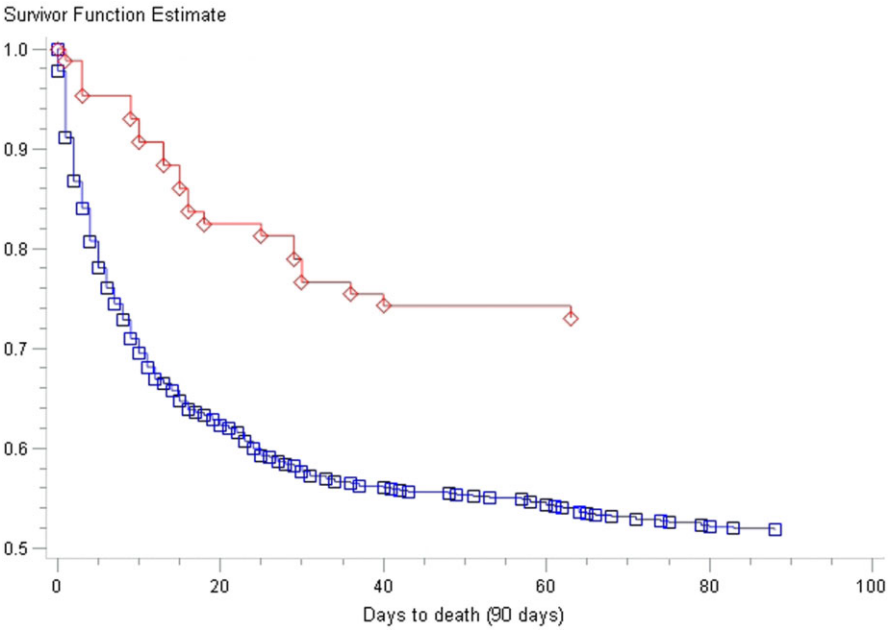

Fig. 1 Multivariate Cox proportional hazard models for 90 day mortality stratified by angiotensin-converting enzyme inhibitor (ACEI) exposure after adjustment for baseline variables. (□) Non-ACEI group, (◊) ACEI group.

DISCUSSION

Our study assessed the association between ACEI use and clinically important outcomes by analysing the data from a large, multicenter randomized trial in critically ill patients with AKI requiring dialysis. We found that ACEI use during the ICU admission was infrequent and that recipients of ACEI differed from other patients in their baseline characteristics. While multivariate models and sensitivity analyses suggested improvements in clinical outcomes with ACEI use, the use of a time-dependent variable analysis suggested these effects were likely due to artefact.

ACEI use in the ICU setting

To our knowledge, there are no clinical studies investigating ACEI use in the setting of AKI requiring haemodialysis. Current literature on use of ACEI in AKI has mainly focused upon patients following cardiac bypass and aortic surgery in the pre-dialysis setting with discordant results.[13–16] Benedetto's analysis of patients undergoing on-pump coronary artery bypass grafting[14] found that ACEI use preoperatively until the day of surgery reduced the incidence of AKI postoperatively. By contrast, a retrospective cohort study[13] demonstrated that preoperative use of ACEI or angio-

Table 3 Time-dependent multivariable Cox proportional hazard models for 90 day mortality for all patients and day 8 subgroup patients

Variables	Unit	All patients		Day 8 subgroup patients	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
ACEI administration	Yes *vs* No	0.78 (0.51–1.21)	0.3	0.80 (0.47–1.34)	0.4
Age (years)	per 1 year older	1.03 (1.02–1.03)	<0.0001	1.03 (0.17–1.04)	<0.0001
Male (%)	Male *vs* women	1.06 (0.86–1.29)	0.6	1.16 (0.87–1.57)	0.3
APACHEIII†	per 10 pts increment	1.05 (1.01–1.09)	0.01	1.01 (0.95–1.07)	0.7
Severe sepsis†	Yes *vs* No	1.01 (0.84–1.22)	0.9	1.25 (0.95–1.66)	0.1
Mechanical ventilation†	Yes *vs* No	1.18 (0.91–1.55)	0.2	1.02 (0.71–1.47)	0.9
Mean SOFA	per 1 pts increment	1.99 (1.68–2.36)	<0.0001	2.30 (1.81–2.91)	<0.0001
Cardiovascular SOFA score	per 1 pts increment	2.04 (1.54–2.69)	<0.0001	2.08 (1.48–2.93)	<0.0001
Haemodialysis	Yes *vs* No	0.82 (0.47–1.43)	0.5	1.35 (0.76–2.40)	0.3
Urine output	per 100 mL increment	0.98 (0.97–0.99)	<0.0001	0.98 (0.97–1.00)	0.006
Serum potassium	per 0.5 mmol/L increment	1.08 (1.00–1.17)	0.06	1.01 (0.88–1.17)	0.9
Serum bicarbonate	per 5 mmol/L increment	0.81 (0.72–0.92)	0.0007	0.98 (0.81–1.18)	0.8
Serum Albumin	per 10 g/L increment	0.95 (0.82–1.11)	0.5	0.93 (0.74–1.18)	0.6
Haemoglobin	per 10 g/L increment	1.04 (0.97–1.11)	0.3	1.04 (0.93–1.17)	0.5

†The data at baseline were used for these variables, because the time-dependent data were not available. ACEI, angiotensin-converting enzyme inhibitor; APACHEIII, acute physiology and chronic health evaluation III; CI, confidence interval; HR, hazard ratio; pts, points; SOFA, sequential organ failure assessment.

tensin receptor blockade appeared to be an independent predictor for AKI and was associated with a 27.6% higher risk for postoperative kidney injury. However, varying study designs, statistical methods and study populations (undergoing differing renal insults) make head-to-head comparisons and the drawing of robust conclusions difficult.

As infectious disease and sepsis is highly prevalent in intensive care units,[17] a number of studies have also investigated the use of ACEI in this setting. One recent study[18] found that preoperative ACEI or angiotensin receptor blockade use in patients undergoing general anaesthesia for high risk elective surgery was associated with a reduction in the incidence of postoperative acute lung injury, possibly through reductions in the release of inflammatory markers such as IL-1β into the bloodstream.[19]

ACEI use in end-stage kidney disease

Despite the widespread use of ACEI to slow progression of CKD, evidence on its use in end-stage kidney disease is sparse. One retrospective study[20] showed that ACEI use was associated with 52% risk reduction in mortality in patients on chronic haemodialysis, with this survival benefit independent of the blood pressure lowering effect and more pronounced in patients 65 years or younger. The FOSIDIAL study[21] is the only randomized, placebo-controlled trial assessing the cardio-protective effect of ACEI in patients receiving chronic haemodialysis. It did not show a significant difference in cardiovascular outcomes (assessed by the composite outcome of cardiovascular death or cardiovascular events) with fosinopril compared with placebo. Most recently,[22] a secondary analysis of the HEMO study suggested that ACEI use was not associated with reductions in all-cause mortality or cardiovascular morbidity. Although there is limited data on the use of ACEI in chronic haemodialysis patients with congestive heart failure, current guidelines still recommend that these agents be used in this subset of dialysis patients.[23]

Study strengths and limitations

To our knowledge, this is the first study assessing association of ACEI and AKI in the dialysis setting using the data from a randomized clinical trial. It uses a large cohort of patients with extensive and prospectively collected baseline data and almost complete follow-up of participants. The major limitation of our study is the presence of confounding by indication, which is a common bias in observational epidemiologic studies of drug effects. For example, the high mortality seen in the early period following randomization in the RENAL study participants meant that the patients who survived this phase had more opportunity for exposure to ACEI. Another limitation is the division of participants into those receiving ACEI and those not receiving ACEI being done post-randomization, giving rise to notable baseline differences between the groups. We therefore employed several analytic techniques to adjust for these potential sources of bias[24] and, in doing so, conclude that there is no survival benefit of ACEI administration.

In conclusion, there is very limited literature exploring the effect of ACEI use in the setting of AKI. In this observational analysis of the RENAL study, the use of ACEI during the follow-up period was infrequent and was not associated with statistically significant impacts upon patient survival. The limited literature on the use of these common medications in AKI requires further data to fully elucidate their effects.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Fig. S1 Kaplan–Meier survival plot from randomisation to day 90 stratified by ACEI exposure.

Table S1 Association of clinical parameters at baseline with the risk for 28 day mortality.

Table S2 Baseline characteristics of study participants surviving ≥8 days by ACEI exposure.

Table S3 Time-dependent multivariable Cox proportional hazard models for 28 day mortality for all patients and day 8 subgroup patients.

Chapter 13

Timing of Renal Replacement Therapy and Patient Outcomes in the Randomized Evaluation of Normal versus Augmented Level of Replacement Therapy Study

Timing of Renal Replacement Therapy and Patient Outcomes in the Randomized Evaluation of Normal Versus Augmented Level of Replacement Therapy Study*

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Objectives: To explore the relationship between timing of continuous renal replacement therapy commencement and clinical outcomes in critically ill patients with acute kidney injury. The primary outcomes were all-cause mortality at 28 and 90 days.

Design: Nested observational cohort study using data from the Randomized Evaluation of Normal Versus Augmented Level Replacement Therapy Study.

Setting: Twenty-three ICUs in Australia and New Zealand.

Patients: Four hundred thirty-nine critically ill patients with acute kidney injury Risk, Injury, Failure, Loss, End-stage kidney disease-injury (RIFLE-I) criteria.

Interventions: None.

Measurements and Main Results: The time between RIFLE-I acute kidney injury and randomization in the Randomized Evaluation of Normal Versus Augmented Level Replacement Therapy Study (proxy for continuous renal replacement therapy commencement) was the variable of interest. All baseline variables in the Randomized Evaluation of Normal Versus Augmented Level Replacement Therapy Study were assessed. Multivariable Cox, logistic, and linear regression models were used to assess the independent relationship of time of onset of RIFLE-I acute kidney injury and randomization and patient outcomes. The median time between RIFLE-I acute kidney injury and continuous renal replacement therapy commencement was 17.6 hours (interquartile range, 7.1–46 hr). Based on four groups of continuous renal replacement therapy commencement ([group 1; reference]: < 7.1, [group 2]: ≥ 7.1 to < 17.6, [group 3]: ≥ 17.6 to < 46.0, [group 4]: ≥ 46.0 hr), earlier commencement of continuous renal replacement therapy was not associated with a significantly lower risk of death at 28 days (hazard ratio for group 2: 1.06, 95% CI: 0.62–1.81; $p = 0.83$; hazard ratio for group 3: 1.23, 95% CI: 0.71–2.12; $p = 0.46$; hazard ratio for group 4: 1.33, 95% CI: 0.77–2.31; $p = 0.31$). Similar findings were observed for death at 90 days.

Conclusions: In a subgroup of participants of the Randomized Evaluation of Normal Versus Augmented Level Replacement Therapy Study, earlier commencement of continuous renal replacement therapy relative to RIFLE-I acute kidney injury was not

***See also p. 1933.**

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The Randomized Evaluation of Normal Versus Augmented Level of Replacement Therapy (RENAL) Study Investigators are listed in **Appendix 1**.

Dr. Jun was responsible for data collection, analysis, interpretation, and article preparation. Drs. Bellomo, Cass, Gallagher, and Lo contributed to study concept design. All authors contributed to data interpretation and critical review of the article. Dr. Bellomo had full access to all data in the study and takes responsibility for the integrity of the data and accuracy of the analysis.

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significantly associated with improved survival. Additional studies with larger sample sizes and broader commencement times are warranted. (*Crit Care Med* 2014; 42:1756–1765)

Key Words: acute kidney injury; continuous renal replacement therapy; timing of continuous renal replacement therapy initiation

Despite substantial advances in our knowledge in the management of critically ill patients, the mortality of acute kidney injury (AKI) remains high. Increasing the intensity of dialysis showed promise (1), but subsequent studies (2, 3) and a meta-analysis (4) have not revealed a mortality benefit from it. Although there has been interest in the timing of dialysis initiation (5, 6), a paucity of clinical trials and lack of consensus regarding the definition and stages of AKI have limited progress. In addition, studies to date have used poor surrogates (urea or creatinine concentration, delay from ICU admission to start of renal replacement therapy [RRT]) instead of actual time of AKI onset to assess the relationship between the timing of RRT commencement and patient outcomes.

The recently published Acute Kidney Injury Network definition of AKI and the Acute Dialysis Quality Initiative published RIFLE (Risk, Injury, Failure, Loss, End-stage kidney disease) criteria, which describe the stages of AKI (7, 8), can assist in exploring the issue of timing in a way that relates initiation of RRT to the actual onset of severe AKI.

In a subgroup of the Randomized Evaluation of Normal Versus Augmented Level (RENAL) Study, we tested the hypothesis that earlier commencement of continuous renal replacement therapy (CRRT) in critically ill patients with AKI improves survival.

METHODS

The RENAL Study was a multicenter, prospective, randomized controlled trial assessing the effect of CRRT intensity in 1,508 critically ill patients with AKI (2). The Human Research Ethics Committees of the University of Sydney and all participating institutions approved the study. The details of the RENAL Study are reported elsewhere (2). In brief, patients were eligible for enrollment if they were adults with AKI in an ICU and considered to require RRT by the treating clinician and satisfied predefined criteria. Eligible patients were randomly assigned to continuous venovenous hemodiafiltration with effluent flow at 40 mL/kg/hr (higher intensity) or 25 mL/kg/hr (lower intensity). The primary outcome of the study was all-cause mortality by day 90.

Selection of Participants Based on the RIFLE Criteria

Of the 35 sites participating in the RENAL Study, 23 agreed to participate in collecting additional patient data according to the RIFLE criteria. The baseline serum creatinine of patients was ascertained based on their previous records, and if more than one measurement was taken, then the latest value before hospital admission was considered as the "normal (pre-illness)" baseline serum creatinine value. For patients with no observed baseline creatinine measurement, a notional baseline glomerular filtration rate of 75 mL/min was allocated to them. These data allowed the derivation of the time at which these study participants met the criteria for renal "injury" (I) using the RIFLE criteria in a subgroup of study patients. The time between meeting the RIFLE criteria for the diagnosis of renal "injury" and randomization in the RENAL Study was used as the variable of interest. The time of study randomization was used as a proxy for CRRT as randomization was typically rapidly followed by CRRT initiation. Additional data on the baseline characteristics of study participants, including demographic, biochemical, and illness severity data, were derived from the original study dataset.

Statistical Analysis

Continuous variables are reported as means with SD for normally distributed variables and as median and interquartile range for nonnormally distributed variables. Timing of CRRT commencement and all available baseline variables, including RENAL study treatment group, previous ICU admission status, where the patient was admitted to ICU from, demographic information (gender, age, and weight), laboratory information (international normalized ratio [INR], activated partial thromboplastin time, hemoglobin, WBC count, platelet count, sodium, potassium, chloride, bicarbonate, urea, serum creatinine, phosphate, albumin, magnesium, pH, base excess, ionized calcium, glucose, Pa_{CO_2}, and glomerular filtration rate), and disease measures (presence of sepsis, mechanical ventilation status, presence of oliguria, presence of acidemia, presence of edema, presence of organ failure, presence of nonrenal organ failure, Sequential Organ Failure Assessment [SOFA] score [total and individual components: coagulation, liver, cardiovascular, and renal scores], and Acute Physiology and Chronic Health Evaluation [APACHE] III scores), were used to construct Cox and logistic regression models. The final models included variables that remained significant in the model after applying the backward stepwise elimination method.

Multivariable logistic regression models were also constructed to test robustness of findings. In all models, to ensure robustness, timing of dialysis commencement was divided into two groups based on the median value and also into four groups based on quartiles. The earliest CRRT commencement group was used as the reference group (< 17.6 hr for two groups; < 7.1 hr for four groups) in all analyses. As part of a series of sensitivity analyses, we also performed the analyses using urea levels as a surrogate for the timing of dialysis commencement. Timing of dialysis commencement was divided into four groups based on urea level quartiles with the lowest urea level group used as the reference group (< 13.6 mmol/L). In addition, multivariable linear regression models were constructed to assess the relationship between timing of dialysis commencement (assessed as a continuous variable) and the following secondary outcomes: ICU-free days, hospital-free days, mechanical ventilation-free days, and CRRT-free days at

90 days follow-up. A mortality event was allocated a value of zero intervention-free days.

In order to adjust for possible selection bias, we performed propensity score analyses as part of additional sensitivity analyses. Propensity scores were calculated using hospital-based characteristics (recruiting site, country, and type of hospital [university, urban, rural, or private]) and all of the previously mentioned patient and laboratory measurements with a multivariable logistic regression model. Multivariable Cox and logistic regression models assessing the relationship between timing of dialysis commencement and all-cause mortality at 28 and 90 days were constructed as above, but also included the calculated propensity scores as a covariate.

We assessed the utility of baseline urea as a marker for AKI and RRT commencement and determined its sensitivity and specificity in comparison to RIFLE-I ("Injury") which we considered here as the "gold standard." We performed subgroup analysis, repeating the analyses in participants who did not have life-threatening indications (defined as the presence of hyperkalemia, acidemia, or edema) for RRT commencement to explore the association between timing of RRT commencement and all-cause mortality in these participants.

A two-sided *p* value less than 0.05 was taken to indicate statistical significance. Statistical analyses were performed using SAS version 9.1 (SAS Institute Inc, Cary, NC) and STATA 9.2 (StataCorp, College Station, TX).

RESULTS

From the 1,508 participants randomized in the RENAL study, we collected RIFLE criteria data in 439 participants (29.1%) (**Supplemental Fig. 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/A901). Of these, 214 (48.7%) had been allocated to receive higher intensity dialysis treatment. The median time from AKI diagnosis to CRRT commencement was 17.6 hours (interquartile range, 7.1–46.0 hr). The baseline characteristics of the 439 participants broken down by quartiles of RRT commencement time are shown in **Table 1**.

Participants with the most prolonged time to CRRT commencement (≥ 46.0 hr) were more likely to be admitted to ICU from a hospital ward, had lower rates of oliguria and acidemia, weighed less, had higher levels of urea, and had lower base excess values when compared with the other groups.

On univariate Cox analysis, earlier commencement of CRRT did not reduce the risk of all-cause mortality at day 28 or day 90 (**Table 2**). The findings from multivariable Cox analysis remained consistent overall, showing no significant reductions in the risk of death at day 28 or day 90 (**Tables 3** and **4**).

However, the hazard ratio (HR) for the outcome of death at day 28 appeared to rise in a graded fashion (from HR 1.06 to 1.33) with progressively delayed CRRT, with the most delayed CRRT commencement group showing the highest HR for harm (HR, 1.33; 95% CI, 0.77–2.31; $p = 0.31$). A similar pattern was observed for the outcome of all-cause mortality at day 90 with the exception of the group commencing CRRT at greater than or equal to 7.1 to less than 17.6 hours (Table 4 and **Fig. 1**). However, there was no statistically significant evidence of a trend toward harm both at day 28 and day 90 ($p = 0.25$ and 0.19, respectively). Similar results were observed on univariate and multivariable logistic analyses (**Supplemental Tables 1–3**, Supplemental Digital Content 2, http://links.lww.com/CCM/A902).

Sensitivity analyses using urea concentrations as the surrogate marker for RRT commencement showed that baseline urea levels at the commencement of RRT was significantly associated with an increased risk of death, both at day 28 and day 90 (**Supplemental Tables 4 and 5**, Supplemental Digital Content 3, http://links.lww.com/CCM/A903) in multivariable Cox analyses. The group with the highest urea concentrations (≥ 32.3 mmol/L) had an 83% increase (95% CI, 1.00–3.34; $p = 0.049$) and more than a two-fold increase (HR, 2.32; 95% CI, 1.39–3.83; $p = 0.001$) in the risk of death at day 28 and day 90, respectively, compared with the lowest urea group (reference group: < 13.6 mmol/L). Similar results were observed for multivariable logistic analyses although statistical significance was not observed for all-cause mortality at day 28 (**Supplemental Tables 6 and 7**, Supplemental Digital Content 4, http://links.lww.com/CCM/A904).

Using multivariable linear regression models to analyze the continuous secondary outcomes, timing of CRRT commencement (assessed as a continuous variable) was not associated with ICU-free days at 90 days ($p = 0.53$; **Supplemental Table 8**, Supplemental Digital Content 5, http://links.lww.com/CCM/A905), hospital-free days at 90 days ($p = 0.07$; **Supplemental Table 9**, Supplemental Digital Content 6, http://links.lww.com/CCM/A906), RRT-free days at 90 days ($p = 0.41$; **Supplemental Table 10**, Supplemental Digital Content 7, http://links.lww.com/CCM/A907), or mechanical ventilation-free days at 90 days ($p = 0.36$; **Supplemental Table 11**, Supplemental Digital Content 8, http://links.lww.com/CCM/A908).

Covariates that significantly predicted an increased risk of death at day 28 and day 90 included SOFA respiratory and liver scores, INR, WBC count, creatinine, magnesium, glucose, age, APACHE III scores, and previous ICU admission status (Tables 3 and 4). Increasing creatinine levels at CRRT initiation were associated with a reduction in the risk of death (Cox regression all-cause mortality at day 28 and day 90, $p = 0.001$ and $p < 0.001$, respectively; Tables 3 and 4). Similarly, increasing glucose levels was associated with a significantly reduced risk of death (Cox regression *p* values for glucose categories = 0.002–0.009) (Table 3).

When the robustness of these findings was assessed in propensity score–adjusted Cox regression models with the CRRT commencement time variable dichotomized, all findings remained essentially unchanged (**Supplemental Table 12** (Supplemental Digital Content 9, http://links.lww.com/CCM/A909). In subgroup analysis exploring the association of RRT commencement and all-cause mortality in participants who did not have hyperkalemia, acidemia, or edema ($n = 141$), similar results were observed where participants with the most prolonged commencement of RRT (> 65.2 hr) had characteristics associated with better prognosis (**Supplemental Table 13**, Supplemental Digital Content

TABLE 1. Baseline Characteristics Grouped by the Time Between Acute Kidney Injury Diagnosis and Randomization

Baseline Characteristics	Time From Acute Kidney Injury Diagnosis to Randomization					Risk, Injury, Failure, Loss, End-Stage Kidney Disease-Injury Cohort in RENAL Study	Remaining RENAL Cohort	
	< 7.1 Hr	≥ 7.1 to < 17.6 Hr	≥ 17.6 to < 46.0 Hr	≥ 46.0 Hr	*p*			*p*
Total number	109	110	109	111		439	1,026	
Study treatment received (*n*/%)								
High-intensity CRRT	54 (49.5)	52 (47.3)	52 (47.7)	55 (49.5)	0.979	213 (48.5)	509 (49.6)	
Standard-intensity CRRT	55 (50.5)	58 (52.7)	57 (52.2)	56 (50.5)		226 (51.5)	517 (50.3)	0.702
Male (*n*/%)	73 (66.9)	69 (62.7)	65 (59.6)	75 (67.6)	0.571	282 (64.2)	664 (64.7)	0.860
Age (yr, SD)	65.5 (13.2)	64.6 (14.2)	63.5 (15.8)	63.9 (14.6)	0.752	64.4 (14.5)	64.5 (15.0)	0.822
Weight (kg, SD)	80.2 (13.8)	79.6 (12.6)	81.1 (13.7)	84.9 (16.1)	0.025	81.5 (14.2)	80.2 (12.2)	0.108
Source of admission (*n*/%)								
Accident and emergency	29/105 (27.6)	41/105 (39.0)	23/102 (22.5)	16/101 (15.8)		109 (26.4)	239 (24.9)	
Hospital floor/ward	23/105 (21.9)	28/105 (26.7)	42/102 (41.1)	50/101 (49.5)		143 (34.6)	244 (25.5)	
Transfer from another ICU	14/105 (13.3)	6/105 (5.7)	6/102 (5.9)	6/101 (5.9)	< 0.001	32 (7.8)	79 (8.2)	0.004
Transfer from another center	11/105 (10.5)	6/105 (5.7)	13/102 (12.7)	7/101 (6.9)		37 (9.0)	117 (12.2)	
Admitted directly from OT/recovery following emergency surgery	16/105 (15.2)	9/105 (8.6)	13/102 (12.7)	17/101 (16.8)		55 (13.3)	151 (15.7)	
Admitted directly from OT following elective surgery	12/105 (11.4)	15/105 (14.3)	5/102 (4.9)	5/101 (5.0)		37 (9.0)	127 (13.2)	
Sepsis (*n*/%)	45 (41.2)	60 (54.5)	59 (54.1)	67 (60.4)	0.036	231 (52.6)	492 (48)	0.105
Mean Sequential Organ Failure Assessment score	1.9 (0.6)	2.1 (0.5)	2.1 (0.6)	2.1 (0.6)	0.099	2.06 (0.6)	2.07 (0.6)	0.729
Acute Physiology and Chronic Health Evaluation III score	104.6 (28.6)	110.2 (25.9)	103.9 (20.6)	95.7 (24.1)	< 0.001	103.6 (25.4)	101.8 (25.7)	0.241

(*Continued*)

TABLE 1. (*Continued*) Baseline Characteristics Grouped by the Time Between Acute Kidney Injury Diagnosis and Randomization

Baseline Characteristics	Time From Acute Kidney Injury Diagnosis to Randomization					Risk, Injury, Failure, Loss, End-Stage Kidney Disease-Injury Cohort in RENAL Study	Remaining RENAL Cohort	
	< 7.1 Hr	≥ 7.1 to < 17.6 Hr	≥ 17.6 to < 46.0 Hr	≥ 46.0 Hr	*p*			*p*
Mechanically ventilated (*n*/%)	79 (72.5)	79 (71.8)	68 (63.0)	80 (72.1)	0.354	306 (69.9)	776 (75.6)	0.021
Oliguria (*n*/%)	67 (61.5)	79 (71.8)	69 (63.3)	35 (31.5)	< 0.001	250 (56.9)	624 (60.8)	0.166
Acidemia (*n*/%)	47 (43.1)	45 (40.1)	38 (34.9)	16 (14.4)	< 0.001	146 (33.3)	375 (36.5)	0.228
Edema (*n*/%)	45 (41.3)	51 (46.4)	55 (50.5)	54 (48.6)	0.557	205 (46.7)	437 (42.5)	0.147
Creatinine (μmol/L)	263 (172–373)	249 (185–374)	318 (251–419)	332 (251–460)	0.0.006	340.2 (201.5)	278 (204–400)	0.288
Urea (mmol/L)	17.2 (10.6–28.6)	17.1 (11–28.5)	20.7 (15.2–31.1)	28.8 (19.6–34.3)	< 0.001	23.8 (13.0)	20.4 (13.7–30.9)	0.723
pH	7.2 (0.2)	7.2 (0.1)	7.3 (0.1)	7.3 (0.1)	< 0.001	7.26 (0.1)	7.25 (0.1)	0.05
Base excess (mmol/L)	−9.8 (7.5)	−8.9 (7.1)	−7.9 (6.3)	−4.5 (6.8)	< 0.001	−7.8 (7.2)	−8.4 (6.8)	0.141
Bicarbonate (mmol/L)	16.9 (5.9)	18.0 (5.7)	18.9 (5.3)	20.9 (6.7)	< 0.001	18.7 (6.1)	18.2 (5.7)	0.131
Outcomes								
Number of deaths at 28 d (*n*/%)	39/109 (35.8)	43/110 (39.1)	40/109 (36.7)	44/111 (39.6)	0.923			
Number of deaths at 90 d (*n*/%)	44/109 (40.4)	47/110 (42.7)	50/109 (45.9)	52/111 (46.8)	0.759			

RENAL = Randomized Evaluation of Normal Versus Augmented Level Replacement Therapy, CRRT = continuous renal replacement therapy, OT = operating theater.

TABLE 2. Univariate Cox Regression Assessing the Relationship Between Renal Replacement Therapy Commencement Time and All-Cause Mortality at Day 28 and Day 90

Variable	All-Cause Mortality at 28 Days			All-Cause Mortality at 90 Days		
	Hazard Ratio	95% CI	*p*	Hazard Ratio	95% CI	*p*
Time from AKI to randomization group 1 (< 7.1 hr)	1.00	–	–	1.00	–	–
Time from AKI to randomization group 2 (≥ 7.1 to < 17.6 hr): group 2 vs group 1	1.08	0.70–1.67	0.723	1.06	0.70–1.60	0.785
Time from AKI to randomization group 3 (≥ 17.6 to < 46.0 hr): group 3 vs group 1	1.02	0.65–1.58	0.940	1.14	0.76–1.71	0.529
Time from AKI to randomization group 4 (≥ 46.0 hr): group 4 vs group 1	1.06	0.69–1.64	0.783	1.13	0.76–1.69	0.542

AKI = acute kidney injury.

Dashes indicate referent values (i.e. the first category [time from AKI to randomization group 1]) is the referent group).

TABLE 3. Multivariable Cox Model for All-Cause Mortality at Day 28

Variable	Hazard Ratio	95% CI	*p*
Time from AKI to randomization group 1 (< 7.1 hr)	1.00	–	–
Time from AKI to randomization group 2 (≥ 7.1 to < 17.6 hr): group 2 vs group 1	1.06	0.62–1.81	0.83
Time from AKI to randomization group 3 (≥ 17.6 to < 46.0 hr): group 3 vs group 1	1.23	0.71–2.12	0.46
Time from AKI to randomization group 4 (≥ 46.0 hr): group 4 vs group 1	1.33	0.77–2.31	0.31
Study treatment (high vs low intensity)	0.91	0.63–1.31	0.61
SOFA respiratory score (per 1-point increase)	1.53	1.20–1.94	< 0.001
SOFA liver score (per 1-point increase)	1.32	1.13–1.55	< 0.001
International normalized ratio (per 1 unit increase)	1.32	1.12–1.57	0.001
WBC count group 1 (< 9.2×10^9/L)	1.00	–	–
WBC count group 2 (≥ 9.2×10^9 to < 13.6×10^9/L): group 2 vs group 1	0.53	0.31–0.90	0.02
WBC count group 3 (≥ 13.6×10^9 to < 18.7×10^9/L): group 3 vs group 1	0.61	0.38–1.00	0.05
WBC count group 4 (≥ 18.7×10^9/L): group 4 vs group 1	0.75	0.47–1.19	0.22
Creatinine (per 100 μmol/L increase)	0.78	0.78–0.78	0.001
Magnesium (per 1 mmol/L increase)	2.30	1.35–3.92	0.002
Glucose group 1 (< 6.1 mmol/L)	1.00	–	–
Glucose group 2 (≥ 6.1 to < 7.4 mmol/L): group 2 vs group 1	0.45	0.27–0.75	0.002
Glucose group 3 (≥ 7.4 to < 9.35 mmol/L): group 3 vs group 1	0.47	0.30–0.76	0.002
Glucose group 4 (≥ 9.35 mmol/L): group 4 vs group 1	0.52	0.32–0.85	0.009
Age (per 5-yr increase)	1.17	1.15–1.18	< 0.001

AKI = acute kidney injury, SOFA = Sequential Organ Failure Assessment.

10, http://links.lww.com/CCM/A910). Multivariable Cox regression showed a progressive, nonsignificantly reduced risk of death with delayed RRT (**Supplemental Tables 14–16**, Supplemental Digital Content 11, http://links.lww.com/CCM/A911).

When baseline urea and RIFLE-I were compared for their utility in determining commencement of RRT, the sensitivity and specificity were 61.1% and 61.6%, respectively (**Supplemental Table 17**, Supplemental Digital Content 12, http://links.lww.com/CCM/A912).

DISCUSSION

Statement of Key Findings

Based on a subgroup of participants from the largest randomized controlled trial (RCT) of AKI treatment, we assessed the

TABLE 4. Multivariable Cox Model for All-Cause Mortality at Day 90

Variable	Hazard Ratio	95% CI	*p*
Time from AKI to randomization group 1 (< 7.1 hr)	1.00	–	–
Time from AKI to randomization group 2 (≥ 7.1 to < 17.6 hr): group 2 vs group 1	0.94	0.61–1.43	0.77
Time from AKI to randomization group 3 (≥ 17.6 to < 46.0 hr): group 3 vs group 1	1.19	0.78–1.84	0.42
Time from AKI to randomization group 4 (≥ 46.0 hr): group 4 vs group 1	1.34	0.87–2.09	0.19
Study treatment (high vs low intensity)	1.04	0.78–1.40	0.79
Sequential Organ Failure Assessment liver score (per 1-point increase)	1.14	1.00–1.30	0.05
Platelet cell count (per 1 unit of 9.2×10^9/L increase)	0.99	0.99–1.00	0.008
Creatinine (per 100 μmol/L increase)	0.81	0.81–0.81	0.0001
Acute Physiology and Chronic Health Evaluation III score (per 5-point increase)	1.09	1.08–1.09	< 0.0001

AKI = acute kidney injury.

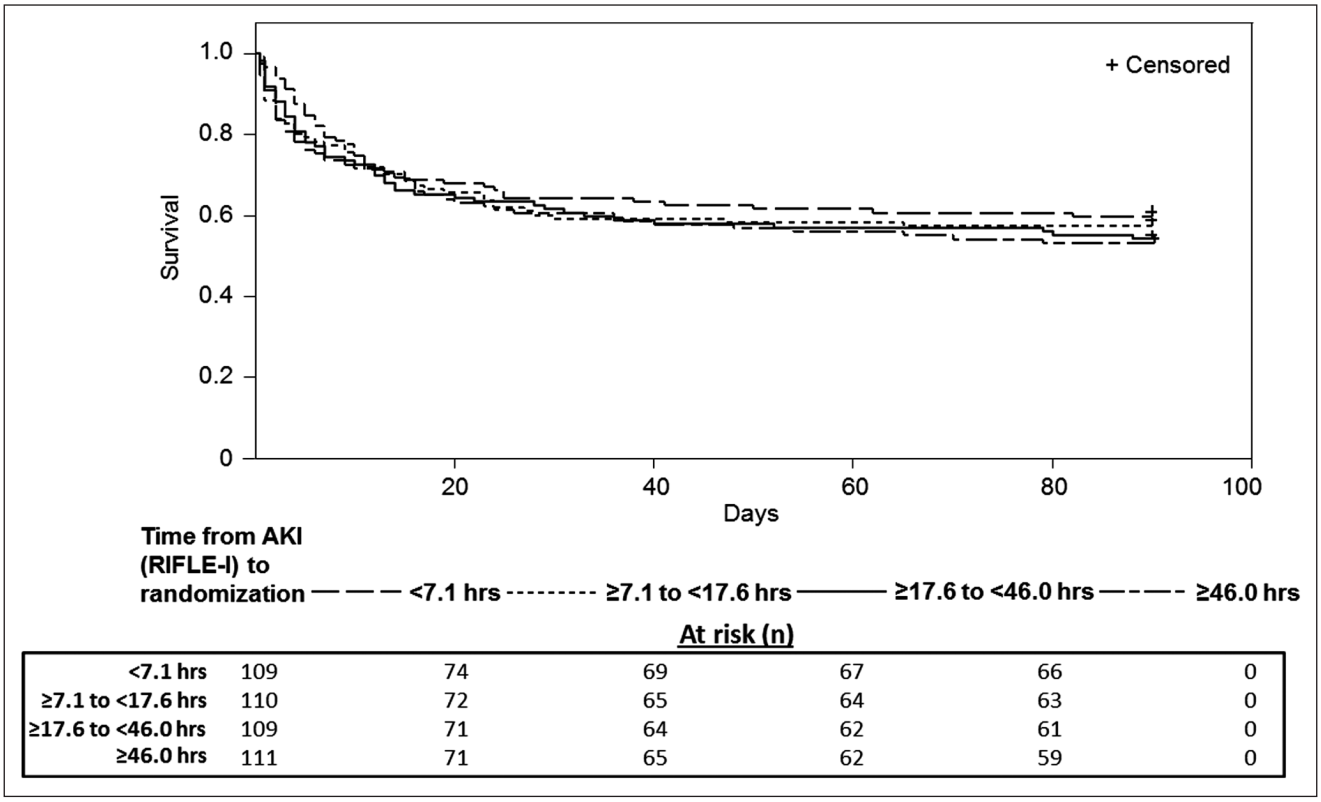

Figure 1. Kaplan-Meier graph of survival plots from randomization to day 90 stratified by timing of continuous renal replacement therapy commencement. RIFLE = Risk, Injury, Failure, Loss, End-stage kidney disease.

association between the timing of CRRT commencement in relation to severe AKI onset defined by RIFLE-I criteria and all-cause mortality at day 28 and day 90. We found that the median time of CRRT initiation was less than 24 hours and that more than three quarters of patients were started on CRRT within 48 hours of developing RIFLE-I. Overall, earlier commencement of CRRT, relative to the onset of RIFLE-I AKI, did not reduce the risk of death at day 28 or day 90. Sensitivity analyses using propensity score–adjusted Cox and logistic regression models did not substantially change the overall results. By contrast, when analyses were repeated using urea concentrations at CRRT commencement, the risk of death was significantly increased with elevated urea concentrations. Based on multivariable Cox and logistics regression models, we observed that the risk of death appeared to progressively (but nonsignificantly) increase with increased delay in RRT commencement. These results did not reach statistical significance. Timing of CRRT initiation was not associated with better secondary outcomes. We compared baseline urea to RIFLE-I to assess its utility as a proxy for RRT commencement and found that its sensitivity and specificity were 61.1% and 61.6%, respectively.

Comparison With Previous Studies

Overall, early commencement of CRRT did not reduce the risk of death. However, the risk of death at day 28 appeared to rise in a graded fashion with progressively delayed CRRT, with the most delayed CRRT commencement group showing the highest HR for harm (HR, 1.33; 95% CI, 0.77–2.31; $p = 0.31$). Consistent observations were made for the outcome of all-cause mortality at day 90. Based on the limited size of our cohort, it may indeed be possible that limited power may have restricted the detection of a significant difference in the effect, if such an effect did exist. When viewed in this light, our overall findings are in keeping with a meta-analysis which included data from four RCTs, one quasi-RCT, and 18 observational studies published since 1961 and suggested a potential advantage from early commencement of CRRT, reporting a nonsignificant point estimate of 36% mortality risk reduction (relative risk, 0.61; 95% CI, 0.40–1.05; $p = 0.08$) from RCT data (9). Among the RCTs, the study with the highest quality score was the study by Bouman et al (10), which used definitions of oliguria and creatinine clearance to randomize 106 critically ill patients with AKI. The study reported no survival benefit with early commencement of dialysis.

Recent observational studies have also suggested elevated mortality rates with delayed commencement of CRRT (6, 11, 12). In particular, the study by Liu et al (6) assessed 243 patients requiring dialysis for severe AKI from the Program to Improve Care in Acute Renal Disease. These investigators estimated the effects of commencing dialysis at lower blood urea nitrogen (BUN) (≤ 76 mg/dL) compared with higher BUN (> 76 mg/dL) on the risk of death within 60 days from AKI diagnosis (6). After adjustment by a range of patient and site characteristics, the study reported an 85% increased risk of death with initiation of dialysis at higher BUN (95% CI, 16–296%). In another study, Wu et al (13) also reported that delayed dialysis, defined as BUN greater than 80 mg/dL, independently predicted an

increased risk of death (odds ratio [OR], 4.01; 95% CI, 1.05–15.27; $p = 0.04$). However, as demonstrated in this study, BUN at the start of CRRT is not a reliable surrogate of actual time between onset of AKI and start of therapy and is confounded by the fact that urea may also act as a marker of catabolism and illness severity. In this regard, our study also found a significant association between urea levels and death but not between actual start relative to the onset of AKI. Nonetheless, in our study, an almost identical OR (1.84) was observed (not statistically significant) when the most delayed CRRT commencement group (≥ 46.0 hr) was compared with the earliest group (< 7.1 hr) in a multivariable logistic regression model determining the mortality risk at day 90.

We found that higher levels of baseline creatinine were associated with better survival, a finding that is consistent with previous reports in the literature (14–18). Lower serum creatinine values prior to CRRT commencement may indicate fluid overload, which is associated with poor outcomes (19). An elevated serum creatinine may also be a surrogate marker of better muscle mass, nutrition, and health (18). Our finding that higher levels of pre-RRT glucose were associated with better survival lends support to this argument.

In a more recent prospective, multicenter, observational study of 1,238 ICU patients with severe AKI, investigators assessed the relationship between the start of RRT relative to the date of ICU admission (5). After adjustment, late RRT (defined by start after 5 d from ICU admission) was associated with a greater than two-fold increase in the odds of death (OR, 2.20; 95% CI, 1.44–3.37; $p < 0.001$). However, the study was limited by differences in AKI diagnosis time points as it was unable to completely discriminate those patients who may have developed AKI later in the course of their ICU stay. Such patients have worse outcomes because they represent failures of ICU treatment to stem the progression of AKI. Indeed, this highlights the challenges of assessing the timing of CRRT commencement, particularly in patients who are admitted to ICU from the ward as these patients may not have had the opportunity to receive CRRT due to differences in the timing of their AKI development. A recent study has attempted to resolve some of these issues by categorizing 98 postoperative patients requiring dialysis to early or late dialysis commencement based on the estimated glomerular filtration rate criteria of the RIFLE criteria (20). Late dialysis was independently associated with an increased risk of in-hospital mortality (HR, 1.85; 95% CI, 1.07–3.18; $p = 0.027$). The above study, however, was limited by its small size, design, and chance of type I error.

Significance of Study Findings

Our study, using a measure of CRRT commencement in relation to onset of severe AKI, could not confirm whether earlier CRRT commencement improves patient survival or delayed CRRT commencement is associated with an increased risk of death. We demonstrated the differential results achieved when using urea-based analyses instead of actual time in relation to onset of AKI. However, graded elevations in the risk of death with delayed CRRT commencement, although not significant, suggest that further assessment of the role of CRRT timing in AKI is strongly warranted. Furthermore, patients with the most delayed CRRT commencement were found to have less disease severity based on lower APACHE III scores and lower rates of clinical symptoms such as oliguria and acidemia, suggesting a selection bias toward delayed CRRT initiation for patients with a perceived lower degree of disease severity. These results were confirmed in further subgroup analyses in participants who did not have life-threatening indications (hyperkalemia, acidemia, and edema) for CRRT commencement. These results suggest that early initiation of RRT in critically ill patients in relation to onset of severe AKI is unlikely to be harmful and also suggest the need to test the hypothesis that earlier commencement of RRT, irrespective of baseline disease severity, may improve patient outcomes. In addition, our trial dataset allowed us the unique opportunity to evaluate the utility of urea as a means of determining the optimal timing of CRRT commencement by assessing the extent to which different urea levels misclassify patients in comparison to RIFLE-I. We found that urea, as a measure of CRRT commencement, has poor sensitivity and specificity, which further highlights the critical limitations of using urea to determine the optimal timing of CRRT in AKI.

Strengths and Limitations

Our study has a number of strengths. Using patient data from a large RCT, this study represents the only cohort of patients so far diagnosed with AKI based on validated RIFLE criteria where timing of CRRT was assessed relative to onset of severe AKI. In addition, all patient data included in all analyses were detailed and prospectively collected. There are, however, several limitations to our study. Due to our sample size, we had limited power to detect a statistical difference in effect, if an effect did indeed exist. Other limitations were a consequence of observational study design. Although we aimed to control for differences in known baseline characteristics using propensity score and covariate adjustments, we could not control for unknown variables not measured as part of the RENAL study. As such, it is possible that selection bias may explain some or all of the results. This study used data from the RENAL study where the initiation of CRRT in relation to ICU admission was early (a mean of < 2 d from admission). Indeed, in the subgroup presented in this study, one quarter of patients commenced CRRT within 7 hours of onset of RIFLE-I. In the only other large RCT of dialysis dose, the mean time of initiation of CRRT was close to 7 days from ICU admission (3). It is possible that, if such a cohort of patients had been studied where timing of CRRT in relation to AKI onset appears likely to be longer, a difference might have emerged. We also acknowledge that AKI onset may have been defined at an earlier time if novel renal biomarkers had been used (21). However, the role of such biomarkers in triggering initiation of CRRT remains undefined. The issue of competing effect of mortality cannot be excluded in the assessment of the association between timing of CRRT commencement and continuous outcomes (ICU-free days, hospital-free days, mechanical ventilation-free days, and CRRT-free days) as a mortality event was allocated a value of

zero intervention-free days. Observational studies such as this one cannot prove causality or lack of causality.

CONCLUSIONS

In a subgroup of participants of the RENAL Study, earlier commencement of CRRT relative to RIFLE-I AKI was not significantly associated with an improved survival. However, nonsignificant graded elevations in the risk of death with progressively delayed CRRT suggest that additional studies with larger sample sizes and broader commencement times are warranted.

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APPENDIX 1. The Randomized Evaluation of Normal Versus Augmented Level of Replacement Therapy (RENAL) Study Investigators

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Chapter 14

Femoral Access and Delivery of Continuous Renal Replacement Therapy Dose

Original Paper

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Femoral Access and Delivery of Continuous Renal Replacement Therapy Dose

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Key Words
Dialysis · Continuous renal replacement therapy · Catheters · Femoral vein · Intensive care

Abstract
Aims: The study aims to describe the use of dialysis catheters in critically ill patients treated with continuous renal replacement therapy (CRRT) and to study the impact of femoral versus non-femoral access on CRRT dose. ***Methods:*** Statistical analysis and predictive modelling of data from the Randomized Evaluation of Normal vs. Augmented Level renal replacement therapy trial. ***Results:*** The femoral vein was the first access site in 937 (67%) of 1,399 patients. These patients had higher Acute Physiology and Chronic Health Evaluation and Sequential Organ Failure Assessment scores ($p = 0.009$) and lower pH ($p < 0.001$) but similar mortality to patients with non-femoral access (44 vs. 45%; $p = 0.63$). Lower body weight was independently associated with femoral access placement (OR 0.97, 95% CI 0.96–0.98). Femoral access was associated with a 1.03% lower CRRT dose ($p = 0.05$), but a 4.20% higher dose was achieved with 13.5 Fr catheters ($p = 0.03$). ***Conclusions:*** Femoral access was preferred in lighter and sicker patients. Catheter gauge had greater impact than catheter site in CRRT dose delivery.
Video Journal Club "Cappuccino with Claudio Ronco" at http://www.karger.com/?doi=439581.

Introduction

The ability to maintain patient homeostasis of water, waste products, electrolytes and acid-base during continuous renal replacement therapy (CRRT) is dependent on CRRT circuit patency over time [1]. The quality of vascular access influences the ability to achieve adequate and reliable blood flow through the circuit, a major determinant of circuit life span. Catheter dysfunction requiring

A complete list of investigators in the RENAL study is provided in the supplementary material (online suppl. item S1; for all online suppl. material, see www.karger.com/doi/10.1159/000439581).

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catheter replacement and/or causing circuit failure occurs in approximately 10% of patients treated with CRRT [2, 3]. Such circuit failures induce interruptions in treatment, which decrease the delivered CRRT dose and uremic control [4]. Moreover, they significantly increase nursing workload and treatment costs [5]. Thus, both choice of optimal insertion site and catheter characteristics are important to delivering optimal therapy.

There is uncertainty regarding the optimal site of catheter insertion for CRRT in critically ill patients. Femoral vein catheterization may be faster and easier than jugular vein catheterization [6] but may impede mobilization [7]. Thus, recent guidelines favor the right jugular vein in preference to femoral veins [8]. These recommendations are, however, not supported by robust evidence. Furthermore, the impact of catheter brand, gauge and length on the delivery of CRRT has only been investigated in small studies and no robust evidence exists to guide choice of catheter.

The Randomized Evaluation of Normal vs. Augmented Level of Replacement Therapy (RENAL) study collected detailed information on dialysis catheter characteristics, site of catheter insertion and circuit anticoagulation during CRRT and therefore offers a unique opportunity to explore the relationship between these factors and delivered CRRT dose [9–11]. Accordingly, we aimed to describe the use of temporary dialysis catheters in intensive care unit (ICU) patients treated with CRRT. In particular, we sought to identify factors associated with choosing the femoral vein as first site of catheter insertion and to explore the association of first insertion site (femoral vs. non-femoral) and different catheter characteristics with delivered CRRT dose during the first full day of treatment.

Materials and Methods

Study Protocol

The RENAL study was a prospective, multicenter, randomized, controlled trial comparing a higher (40 ml/kg/h) versus a lower (25 ml/kg/h) CRRT dose in 1,508 critically ill patients. The Human Research Ethics Committees of the University of Sydney and of all participating institutions approved the study. Written informed consent was obtained from patients or next of kin. Adult patients (≥18 years) with severe AKI requiring acute RRT were included if they met at least one of the following criteria: oliguria (urine output <100 ml during ≥6 h not responding to fluid resuscitation), hyperkalemia (serum potassium >6.5 mmol/l), severe acidosis (pH <7.2), a serum urea level >25 mmol/l, a serum creatinine level >300 μmol/l or the presence of clinically significant organ edema. Patients with previous RRT during the same hospitalization or those with end-stage renal failure requiring chronic dialysis were excluded. A detailed study protocol is found in the appendix of the original study [11]. The primary end point was 90-day mortality. Secondary end points included RRT-free days, mechanical ventilation-free days, ICU-free days and hospital-free days at 90-day follow-up.

The site of dialysis catheter insertion, catheter choice and mode of circuit anticoagulation were determined by the treating physician. For the purpose of the present study, the delivered CRRT dose (as a percentage of prescribed dose) during the first complete 24-hour day was recorded.

Statistical Analysis

Data was analyzed by using SAS software version 9.1. Continuous variables were expressed as mean (SD) and categorical variables as numbers (%). The Student t test or the Mann–Whitney test was used to compare continuous variables. The χ^2 test or the Fisher's exact test was used to compare categorical variables. Multivariate logistic regression analysis was used to study the association of having the femoral vein as first site of catheter insertion. Baseline variables were considered and were included in the multivariate model if they were statistically significant at p value <0.20 in the univariate analysis. The association between using a femoral catheter (vs. a non-femoral catheter) and CRRT dose during the first complete 24 h was assessed by multivariate linear regression analysis. The following potential confounders were considered: treatment group, baseline characteristics, illness severity, catheter gauge, catheter length, catheter brand, CRRT machine and anticoagulation mode. Covariates were included in the multivariate model if they were statistically significant at p value <0.20 in the univariate analysis. In the final analyses, a 2-sided p value <0.05 was considered statistically significant.

Results

First Site of Catheter Insertion

Of the 1,508 randomized patients in the RENAL trial, data on first dialysis catheter insertion site was available for 1,399 (93%) patients. In 937 (67%) of these 1,399 patients the femoral vein was chosen as the first site of dialysis catheter insertion (fig. 1). The right femoral vein was preferred over the left. Jugular access was used in 351 (25%) patients and subclavian access was chosen in 111 (8%) patients.

Factors Associated with Femoral Vein Catheterization

Demographics, admission diagnosis, time from ICU admission to randomization, treatment group, baseline biochemistry and outcomes for patients with femoral and non-femoral vein as first site of dialysis catheter insertion are detailed in table 1. Patients receiving femoral access weighed on an average 3.8 kg less than patients receiving a non-femoral access ($p < 0.001$; table 1) and had higher Acute Physiology and Chronic Health Evaluation (APACHE) III scores, cardiovascular Sequential Organ Failure Assessment scores, hemoglobin levels and chlo-

Table 1. Characteristics of patients according to first site of catheter insertion

Characteristic	Femoral (n = 937)	Non-femoral (n = 462)	p values
Age, years	64.3±15.2	65.0±14.2	0.5
Male sex	593 (63.3)	307 (66.5)	0.3
APACHE III score	103.5 (25.7)	100.1 (25.4)	0.02
Time from ICU admission to randomization, h	46.1±105	62.5±145	0.02
Randomized to high CRRT intensity	456 (48.7)	236 (51.1)	0.40
Estimated glomerular filtration rate, ml/min	57.5±31.1	54.7±30.6	0.2
Body weight, kg	79.5±12.5	83.3±13.4	<0.001
Mechanical ventilation	681 (72.7)	356 (77.1)	0.08
Severe sepsis at baseline	473 (50.5)	213 (46.1)	0.1
Non-operative admission diagnosis	695 (74.2)	303 (65.6)	0.6
Operative admission diagnosis	242 (25.8)	159 (34.4)	0.6
Severe acidemia (pH <7.2)	361 (38.5)	132 (28.6)	<0.001
Severe organ edema	421 (44.9)	200 (43.3)	0.6
Cardiovascular SOFA score	2.9 (1.5)	2.7 (1.6)	0.009
INR, %	1.8±1.0	1.7±1.0	0.06
APTT, s	45.8±23.9	46.3±25.3	0.7
Hemoglobin, g/l	100.7±20.1	97.8±18.8	0.008
Platelet count, $\times 10^9$/l	183.6±131	184.3±133	0.9
Sodium, mmol/l	137.3±6.5	138.3±6.7	0.01
Chloride, mmol/l	105.0±7.4	104.1±8.0	0.05
CRRT dose during the first complete 24 h, ml/kg/h	27.5±8.2	26.2±8.3	0.01
Delivered/prescribed CRRT dose during the first complete 24 h, %	85.4±17.4	81.9±19.8	0.002
Duration first catheter/total CRRT time, %	96.6±54.9	94.5±84.2	0.58
Death in ICU	328 (35.0)	151 (32.7)	0.4
Death at day 90	410 (43.8)	208 (45.1)	0.6

Variables are given as mean ± SD or as numbers (percentage). APTT = Activated partial thromboplastin time; INR = international normalized ratio.

ride levels. CRRT was initiated 46.5 h after ICU admission in patients with femoral access and after 62.5 h in patients with non-femoral access (p = 0.02). The first femoral access was used during 96.6% of the total CRRT time and the first non-femoral access was used during 94.5% of the total CRRT time (p = 0.58; table 1). Overall, 410 (44%) patients with a femoral dialysis catheter as first access had died at 90 days after randomization compared with 208 (45%) non-femoral access patients (table 1).

Several factors were associated with a greater likelihood of the use of a femoral vein as the first site of catheter insertion on univariate logistic regression analysis. On multivariate logistic regression analysis, however, only body weight (OR 0.97 for each kg increase, 95% CI 0.96–0.98), sodium levels (OR 0.93 for each mmol increase, 95% CI 0.90–0.96) and chloride levels (OR 1.08 for each mmol increase, 95% CI 1.05–1.11) were independently associated with choosing the femoral vein as the first site of access (table 2).

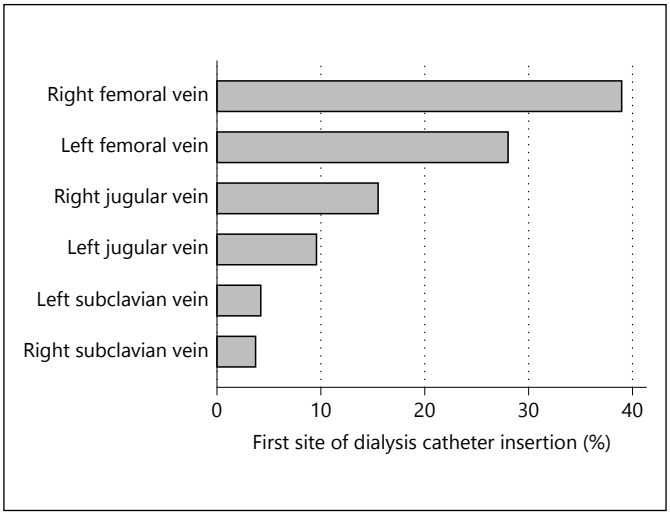

Fig. 1. Site of first temporary dialysis catheter insertion in the RENAL trial (n = 1,399).

Table 2. Univariate and multivariate logistic regression analysis of femoral vein as first site of catheter insertion

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p values	OR (95% CI)	p values[a]
Body weight, kg	0.977 (0.97–0.99)	<0.001	0.972 (0.96–0.98)	<0.001
Sodium, mmol/l	0.979 (0.96–1.00)	0.01	0.928 (0.90–0.96)	<0.001
Chloride, mmol/l	1.015 (1.00–1.03)	0.05	1.078 (1.05–1.11)	<0.001

[a] Adjusted for baseline characteristics with $p < 0.20$ in the univariate analyses. Only variables with $p < 0.05$ in the multivariate analysis are shown.

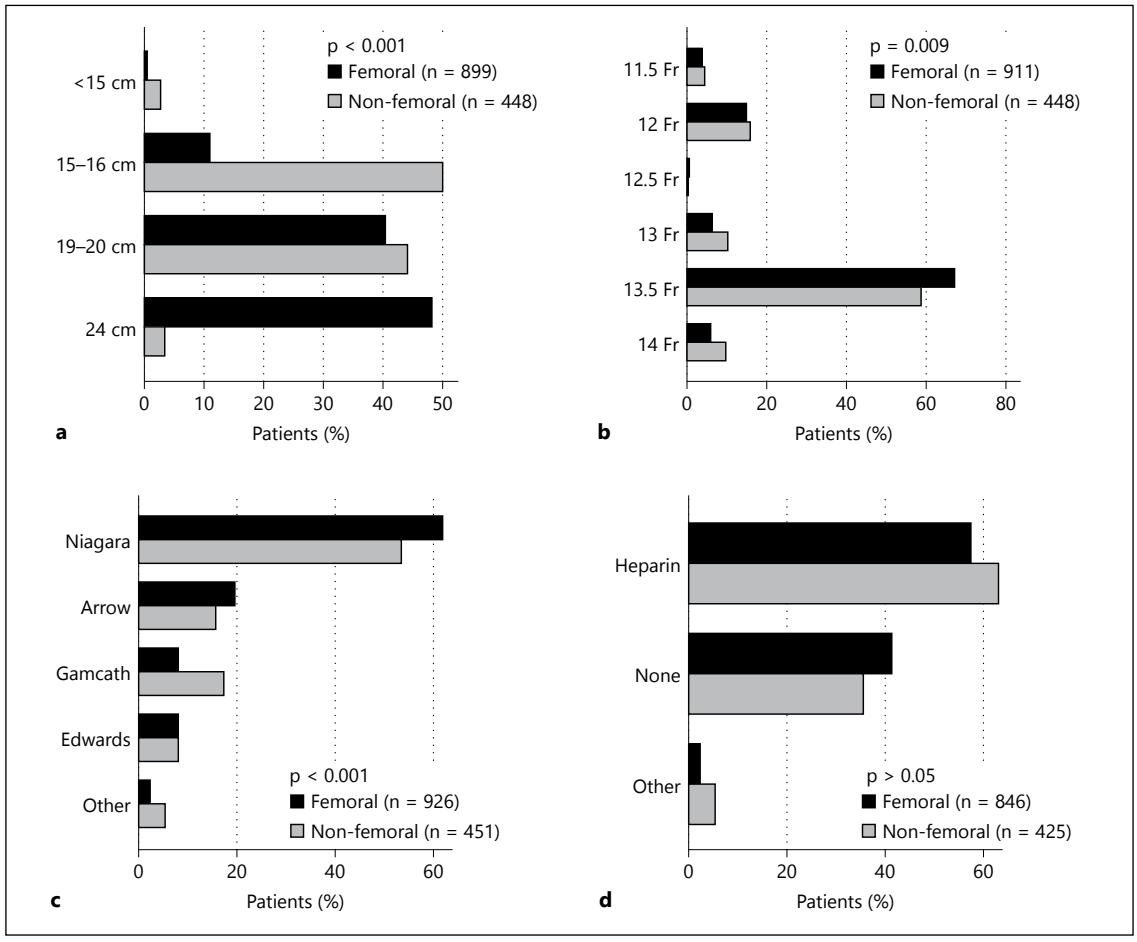

Fig. 2. Length (**a**), gauge (**b**) and brand (**c**) of dialysis catheter as well as circuit anticoagulation (**d**) during CRRT in the RENAL trial according to first site of catheter insertion.

Catheter Characteristics and Circuit Anticoagulation

Longer catheters were generally used for femoral access, whereas shorter catheters tended to be inserted in non-femoral sites (fig. 2a). A 13.5-Fr catheter was most commonly chosen for both femoral (68%) and non-femoral access (59%; fig. 2b). Longer and greater gauge Niagara (Bard, Murray Hill, N.J., USA) catheters were mainly used in the femoral (62%) and non-femoral (53%) group (fig. 2c).

Information on circuit anticoagulation was available for 1,271 (91%) patients. Heparin was used in 487 (58%)

Table 3. Multivariate linear regression showing the association with delivered CRRT dose (as % of prescribed dose) during the first complete 24-hour period

Variable	Coefficient, ±SE	p values[a]
Femoral catheter (vs. non-femoral)	−1.03±0.53	0.05
13.5 French catheter (vs. other gauges)	4.20±1.90	0.03
20- or 24-cm catheter (vs. other lengths)	1.88±1.68	0.3
Randomized to higher CRRT intensity	−26.32±1.27	<0.001

[a] Adjusted for age, sex, APACHE III score, body weight, oliguria, hyperkalemia, acidemia, oedema, urea, creatinine, catheter brand, CRRT machine use and mode of circuit anticoagulation.

of 846 of patients in the femoral group and 269 (63%) of 425 patients in the non-femoral group. CRRT was delivered without circuit anticoagulation in a high proportion of patients with femoral (41%) and non-femoral (36%) catheters (p = 0.50; fig. 2d).

Factors Associated with Delivered CRRT Dose during the First 24 h

A total of 456 (48.7%) patients with a femoral access were randomized to high intensity therapy (40 ml/kg/h) compared to 236 (51.1%) patients with a non-femoral catheter (p = 0.40). On an average, CRRT intensity during the first complete 24 h was 27.5 ml/kg/h in the femoral group and 26.2 ml/kg/h in the non-femoral group (p = 0.01). On an average, 85.4 and 81.9% of the prescribed dose (p = 0.002), respectively, was achieved during this period (table 1). On multivariate linear regression, adjusting for baseline characteristics, treatment group, catheter characteristics, CRRT machine and mode of circuit anticoagulation, the use of a femoral catheter was associated with a 1.03% lower CRRT dose (p = 0.05) during the first 24 h than when a non-femoral catheter was used (table 3). In contrast, a 4.20% higher CRRT dose was achieved with 13.5 Fr gauge catheters than with other catheter gauges (p = 0.03). Finally, being randomized to higher intensity CRRT was independently associated with a 26.32% lower CRRT dose than being allocated to lower intensity CRRT.

Discussion

Key Findings

We analyzed the use of temporary dialysis catheters, the choice of insertion site, the catheter gauge and their impact on CRRT dose in critically ill patients enrolled in the RENAL trial. We found that the femoral vein was used as the first site of dialysis catheter insertion in two thirds of patients and was preferentially chosen in patients with lower body weight and in sicker patients. Using a femoral vein for vascular access had limited impact on the delivered early CRRT dose during the first 24 h. In contrast, catheter gauge was a more important determinant of delivered CRRT dose during this time frame.

Relationship to Previous Studies

Previous studies investigating the impact of vascular access site on delivered RRT dose have reported inconsistent results. Hryszko et al. [12] found an independent 5-fold higher risk of catheter dysfunction, defined as inability to maintain blood flow of at least 150 ml/h, with femoral as compared to internal jugular catheters. In that study, however, 75% of patients were fully mobile, and treatment was with intermittent hemodialysis. Liangos et al. [13] explored dialysis performance during >400 intermittent hemodialysis sessions in 81 patients with acute renal failure. Use of a femoral access, as compared to a non-femoral access, was independently associated with lower urea reduction ratio with intermittent hemodialysis. Of note, however, the femoral catheters used in this study were short, measuring only 16.5 or 19.5 cm. To optimize blood flow and CRRT dose and to avoid recirculation, it is important that the catheter tip is placed in a large vein (external iliac and close of inferior vena cava) or in the right atrium [5, 14, 15]. Therefore, it is recommended that 24-cm catheters be used in the femoral position, and that 15–20 cm catheters be used for right jugular cannulations [16]. In 11 of the 12 centers involved in the French Cathedia study, 16-cm catheters were used in the jugular and 25-cm catheters in the femoral position [17]. Similarly, 24-cm catheters were frequently used for femoral (48%) and 15- to 16-cm catheters were frequently used for jugular or subclavian access (50%) in the RENAL study patients.

The Cathedia study showed a higher rate of catheter-related infections with a femoral access in patients with

body mass index >28.4 kg/m^2 [17]. Furthermore, the increased catheter-related infections risk in heavier patients (>90 kg) with femoral dialysis catheters was recently confirmed in an observational study involving 458 patients [18]. It is therefore not surprising that RENAL study patients receiving right or left femoral catheterization [19] had a lower body weight than patients receiving non-femoral catheterization.

Implications of Study Findings

Our study suggest that clinicians perceive the femoral vein to be a useful potential first choice when rapid and safe access is needed and in patients with a multilumen central venous catheter in the right jugular vein [6]. Our results reflect this preference with sicker patients (more severe acidemia, higher APACHE III and cardiovascular Sequential Organ Failure Assessment score and faster initiation of CRRT after ICU admission) being more likely to have their first CRRT catheter inserted in the femoral vein. This, in turn, may reflect the fact that a central venous catheter is often inserted before a temporary dialysis catheter in hemodynamically unstable patients. Under such circumstances, the femoral route may be the only available option. Finally, we found that a femoral vein is preferred in patients with lower body weight. Although we did not assess body habitus, this finding may reflect the fact that femoral vein cannulation may be technically difficult and is therefore avoided in obese patients. In the univariate comparison, the delivered CRRT dose (as a percentage of the prescribed dose) was 3.5% higher through a femoral access than through a non-femoral access (table 1). A femoral access was, however, associated with 1.03% lower CRRT delivery in the multivariate linear regression analysis. The fact that a higher proportion of patients with femoral access were cannulated with large-gauge 13.5 Fr catheters as compared to patients with non-femoral access (67.5 vs. 59.2%, p = 0.009) likely explains the reversed result in the multivariate adjusted analysis. In fact, after adjusting for several potentially important confounders of the relationship between access site and dose, larger catheter gauge (13.5 Fr) was independently associated with delivery of a higher (4.2%) CRRT dose whereas the ability to achieve the prescribed dose was, as could be expected, impaired in patients allocated to higher intensity CRRT. These findings need to interpreted in the light of the original RENAL trial results. In the RENAL trial, the high-intensity group received a 50% higher CRRT dose than the low-intensity group. Despite this difference in dose, 90-day mortality was similar in both the groups. Our results therefore suggest that insertion of 13.5 Fr gauge CRRT catheters in the femoral vein of very sick critically ill patients have no clinically important negative impact on early CRRT delivery. This is an important finding since femoral catheter insertion is a safer and easier approach for less experienced, junior doctors than cannulation of internal jugular or subclavian veins.

Strengths and Limitations

This study has important strengths. All study data, including highly detailed information on catheter characteristics, insertion site and CRRT dose were prospectively collected. In addition, the large study size enabled adjustment for numerous factors such as patient characteristics, catheter features and mode of anticoagulation, which may potentially affect CRRT delivery. With such adjustments, important practical observations emerged, which can be used to inform clinical practice.

This study has limitations. Choice of catheter insertion site and gauge were not randomized. However, our study provides the largest description of CRRT catheter characteristics, gauge and site of insertion to date and detailed information to adjust for many key early confounders. No information on catheter tip placement was available. However, since longer catheters were used in the femoral position and since non-femoral catheters were mainly inserted in the right jugular vein, it is likely that most of the catheters were positioned correctly. Our study does not provide information on the impact of insertion site or gauge on CRRT delivery beyond the first complete 24 h. This was, however, our intention since determinants of CRRT dose unrelated to access, such as interruptions for investigations, operations and mortality would create a strong competing risk-related confounding effect, given that femoral catheters were inserted in sicker patients. By restricting the analysis to the first complete 24 h of CRRT, we aimed to diminish the impact of such confounders.

Conclusions

The femoral vein was used as the first site of dialysis catheter insertion in most patients within the RENAL trial, especially in lighter and sicker patients. Although such use of a femoral access was significantly associated with lower CRRT dose, the impact on dose was limited. However, using a larger gauge catheter was independently as-

sociated with the ability to deliver a higher CRRT dose during the first 24 h. This information provides clinically relevant information to assist clinicians in their choice of preferred access site and catheter gauge for the delivery of CRRT in critically ill patients.

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Contributions

Research idea and study design: R.B., A.C., M.G.; data analysis/interpretation: J.M., R.B., S.L.; statistical analysis: S.L.; supervision and mentorship: R.B.; drafting of manuscript: J.M., K.M.K., R.B. Each author contributed important intellectual content during manuscript revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. R.B. and M.G. take responsibility that this study has been reported honestly, accurately and transparently; that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained.

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Chapter 15

Epidemiology of RBC Transfusions in Patients with Severe Acute Kidney Injury: Analysis from the Randomized Evaluation of Normal versus Augmented Level Study

Epidemiology of RBC Transfusions in Patients With Severe Acute Kidney Injury: Analysis From the Randomized Evaluation of Normal Versus Augmented Level Study*

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***See also p. 1014.**

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A complete list of investigators in the Randomized Evaluation of Normal versus Augmented Level Replacement Therapy study is provided in the **supplemental data** (Supplemental Digital Content 1, http://links.lww.com/CCM/B562).

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The Randomized Evaluation of Normal Versus Augmented Level Replacement Therapy (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.

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Objective: To assess the epidemiology and outcomes associated with RBC transfusion in patients with severe acute kidney injury requiring continuous renal replacement therapy.

Design: Post hoc analysis of data from a multicenter, randomized, controlled trial.

Setting: Thirty-five ICUs in Australia and New Zealand.

Patients: Cohort of 1,465 patients enrolled in the Randomized Evaluation of Normal versus Augmented Level replacement therapy study.

Interventions: Daily information on morning hemoglobin level and amount of RBC transfused were prospectively collected in the Randomized Evaluation of Normal versus Augmented Level study. We analyzed the epidemiology of such transfusions and their association with clinical outcomes.

Measurements and Main Results: Overall, 977 patients(66.7%) received a total of 1,192 RBC units. By day 5, 785 of 977 transfused patients (80.4%) had received at least one RBC transfusion. Hemoglobin at randomization was lower in transfused than in nontransfused patients (94 vs 111 g/L; $p < 0.001$). Mean daily hemoglobin was 88 ± 7 and 99 ± 12 g/L in transfused and nontransfused patients. Among transfused patients, 228 (46.7%) had

died by day 90 when compared with 426 (43.6%) of nontransfused patients ($p = 0.27$). Survivors received on average 316 ± 261 mL of RBC, whereas nonsurvivors received 302 ± 362 mL ($p = 0.42$). On multivariate Cox regression analysis, RBC transfusion was independently associated with lower 90-day mortality (hazard ratio, 0.55; 95% CI, 0.38–0.79). However, we found no independent association between RBC transfusions and mortality when the analyses were restricted to patients surviving at least 5 days (hazard ratio, 1.29; 95% CI, 0.90–1.85). We found no independent association between RBC transfusion and renal replacement therapy–free days, mechanical ventilator–free days, or length of stay in ICU or hospital.

Conclusions: In patients with severe acute kidney injury treated with continuous renal replacement therapy, we found no association of RBC transfusion with 90-day mortality or other patient-centered outcomes. The optimal hemoglobin threshold for RBC transfusion in such patients needs to be determined in future randomized controlled trials. (*Crit Care Med* 2016; 44:892–900)

Key Words: acute kidney injury; critical care; continuous renal replacement therapy; intensive care; renal failure; transfusion

Anemia triggering RBC transfusions is common in ICU patients (1–3). Although restoring RBCs is inevitable in bleeding patients, the majority of transfusions in ICU are not in response to hemorrhage (3, 4). Observational data suggest that transfusion of RBCs in response to the anemia of critical illness is associated with increased morbidity, especially severe healthcare-associated infections (5) and mortality (6).

In keeping with the above observational studies, previous trials indicate that a restrictive transfusion strategy targeting lower hemoglobin levels is safe in general ICU patients and after cardiac surgery (7–10). However, patients with severe acute kidney injury (AKI) treated with continuous renal replacement therapy (CRRT), a subgroup of patients particularly prone to anemia due to impaired erythropoiesis, fluid overload–associated hemodilution, and CRRT-associated blood loss, may differ in their need for and response to RBC transfusion. In this regard, in such patients, a hemoglobin level below 90 g/L was reported to be independently associated with higher mortality in a study of more than 200 patients (11), prompting uncertainty on how best to respond to anemia in this setting (12).

Because of its size and the unique availability of detailed daily data on hemoglobin levels and RBC transfusion, the Randomized Evaluation of Normal versus Augmented Level of Replacement Therapy (RENAL) study (13–16) offers the opportunity to investigate the relationship between RBC transfusions and clinical outcomes in AKI patients treated with CRRT. Accordingly, we conducted a secondary analysis of the RENAL trial with the aim to describe current transfusion practice in CRRT-treated AKI patients and to explore the association between RBC transfusion, hemoglobin levels, and outcomes in such patients. We hypothesized that, similar to other ICU patients and contrary to small studies, RBC transfusion would be independently associated with unfavorable outcomes in CRRT-treated patients from the RENAL trial.

MATERIALS AND METHODS

Study Description

The RENAL study was a prospective, multicenter, randomized, controlled trial evaluating two intensities of CRRT. The Human Research Ethics Committees of the University of Sydney and of all participating institutions approved the study. Written informed consent was obtained from patients or next of kin. The study was conducted from December 30, 2005, to November 28, 2008, with 1,508 patients randomized to higher (40 mL/kg/hr) versus lower (25 mL/kg/hr) intensity therapy. The main inclusion criteria were critical illness, 18 years old or older, AKI requiring RRT considered by the treating physician. At least one of the following criteria should also be met: urine output less than 100 mL during a 5-hour period without response to fluid resuscitation, a serum potassium level greater than 6.5 mmol/L, a pH less than 7.2, a serum urea level greater than 25 mmol/L, a serum creatinine level greater than 300 µmol/L or the presence of clinically significant organ edema (e.g., pulmonary edema assessed clinically and/or by radiology, or peripheral edema assessed by palpation). Patients with previous RRT during the same hospitalization or with end-stage renal failure requiring chronic dialysis were excluded from the study. Detailed inclusion and exclusion criteria along with study protocol are published the appendix of the main study [13]. The primary endpoint (90-d mortality) was identical (44.7%) in patients treated with high or low CRRT intensity. In addition, no significant differences in secondary endpoints, including RRT-free days, mechanical ventilator–free days, ICU-free days, and hospital-free days at 90-day follow-up, were found.

The decision to transfuse RBCs during the study period was left to the discretion of the treating clinician. According to the study protocol, data on RBC transfusion (number of units and volume [mL] transfused) following randomization until death, ICU discharge, or until day 28 post randomization, whichever occurred first, were recorded daily. Hemoglobin levels were recorded daily as measured with morning blood tests between 4 and 6 AM each day during the same period. No data on RBC transfusions were obtained prior to study inclusion. All red cells were leukodepleted at the source.

Statistical Analysis

Statistical analyses were performed using SAS software version 9.1. Data were summarized as mean (SD) or as proportions. Continuous variables were compared using the Student *t* test or Mann-Whitney *U* test, as appropriate. Categorical variables were compared using the chi-square test or Fisher exact test. Analysis of time to death within 90 days of randomization was assessed using the Kaplan-Meier product limit estimates. Survival curves were compared using the log-rank test. Different propensity score–adjusted multivariate Cox regression analyses were used to study the association between RBC transfusion (vs no RBC transfusion or in milliliters, respectively) and

90-day mortality. Propensity scores for receiving RBC transfusion were estimated from hospital characteristics variables (rural, metropolitan, and university). In addition, we estimated a propensity score from hospital characteristics variables together with all available patient baseline characteristics. The patient baseline characteristics variables used for this propensity score estimation are listed at the end of **Supplementary Table 4** (Supplemental Digital Content 1, http://links.lww.com/CCM/B562). Patients were then divided into four strata based on the quartile of the estimated probabilities of receiving a RBC transfusion. Finally, this estimated probability variable was included as a covariate in the multivariate Cox regression analyses. In addition, we repeated the analysis without the propensity score by forcing all available baseline characteristics into the model.

To test the robustness of any association between RBC transfusion (dichotomized and continuous) and 90-day mortality, we performed logistic regression analyses adjusting for the following variables: median daily calorie intake during ICU admission (high vs low), mean daily calorie intake during ICU admission (continuous), median daily protein intake during ICU admission (high vs low), mean daily protein intake during ICU admission (continuous), mean fluid balance, positive mean fluid (yes vs no), fluid overload at randomization, treatment allocation, age, weight, time from ICU admission to randomization, severe sepsis, Sequential Organ Failure Assessment (SOFA) respiration score, SOFA coagulation score, SOFA liver score, SOFA cardiovascular score, SOFA renal score, overall SOFA score, presence of nonrenal SOFA score, serum creatinine, international normalized ratio, hemoglobin, platelet count, sodium, albumin, magnesium, pH, $PaCO_2$, use of mechanical ventilation.

To remove the confounding effect of early mortality in the analyses and to perform a sensitivity analysis, we a priori decided to restrict further analyses to those patients surviving until a time when the majority (> 80%) of transfused patients had already received RBCs. We then repeated the regression analyses excluding patients who died before this timepoint.

We used multivariate time-dependent Cox regression analysis to assess the effect of daily RBC transfusion volumes on 28-day survival, adjusting for time-varying covariates (CRRT, hemoglobin level, and positive fluid balance) and fixed baseline covariates. We repeated these time-dependent analyses after excluding early deaths.

Multivariate linear regression analyses were used to assess the association between RBC transfusion and secondary outcomes at 90-day follow-up (RRT-free days, mechanical ventilator–free days, ICU-free days, and hospital-free days).

A two-sided p value of less than 0.01 was considered statistically significant due to multiple comparisons

RESULTS

Epidemiology of RBC Transfusion

Of the 1,508 patients randomized in the RENAL trial, data on RBC transfusions were available in 1,465 patients (97.1%). During ICU admission, 977 patients (66.7%) received a total of 1,192 RBC units, whereas 488 patients (33.3%) were not transfused (**Table 1**). By day 5, 785 of 977 transfused patients (80.4%) had received at least one RBC transfusion (Table 1).

Baseline Characteristics of Transfused and Nontransfused Patients

Baseline characteristics and outcomes of transfused and nontransfused patients are compared in **Table 2** and in **Supplementary Table 1** (Supplemental Digital Content 1, http://links.lww.com/CCM/B562). Transfused and nontransfused patients had similar Acute Physiology and Chronic Health Evaluation III score and around half of the patients in each group had severe sepsis at randomization ($p = 0.54$). When compared with patients not being transfused, transfused patients were younger, were more likely to have edema at randomization, were more frequently mechanically ventilated, had lower baseline creatinine levels, and were randomized later in the ICU course. In addition, small but significant differences in baseline coagulation parameters were found.

Hemoglobin Levels

Hemoglobin at randomization was significantly lower in transfused than in nontransfused patients (94 vs 111 g/L; $p < 0.001$). Mean daily hemoglobin was 88 ± 7 and 99 ± 12 g/L ($p < 0.001$) in transfused and in nontransfused patients, respectively, during the study period. For nontransfused patients, hemoglobin concentration decreased by a mean of 2.5 g/L/d for the first 3 days after randomization and remained relatively stable thereafter. For transfused patients, hemoglobin concentration decreased by a mean of 1.2 g/L/d during the first 3 days and remained virtually unchanged thereafter (**Fig. 1**). Baseline characteristics and outcomes in patients with randomization hemoglobin below and above median are summarized in **Supplementary Table 3** (Supplemental Digital Content 1, http://links.lww.com/CCM/B562). When compared with patients with higher hemoglobin, more patients with a hemoglobin below the median were admitted after surgery. They had lower Acute Physiology and Chronic Health Evaluation III score, were less acidotic, were randomized later, and had more often edema at inclusion. Mortality was similar in the two groups. In contrast, the group with lower hemoglobin stayed longer in ICU and in hospital.

Survivors and Nonsurvivors

Among transfused patients, 228 (46.7%) had died by 90 days after randomization when compared with 426 of nontransfused patients (43.6%) ($p = 0.27$; Table 2). The characteristics of survivors and nonsurvivors are compared in **Supplementary Table 2** (Supplemental Digital Content 1, http://links.lww.com/CCM/B562). Survivors received on average 316 ± 261 mL of RBCs, whereas nonsurvivors received 302 ± 362 mL ($p = 0.42$) in the ICU. The volume of transfused RBC was similar between survivors and nonsurvivors over time (**Fig. 2**).

TABLE 1. Cumulative Number of Patients Receiving RBC Transfusions and Number of RBC Units Transfused During ICU Admission or Until Day 28

Variable	First 3 d	First 4 d	First 5 d	First 14 d	ICU Stay or Until Day 28
No. of patients receiving RBC transfusions/all patients, *n* (%)	630/1,465 (43.0)	720/1,465 (49.1)	785/1,465 (53.6)	968/1,465 (66.1)	977/1,465 (66.7)
No. of patients receiving RBC transfusions/ no. of transfused patients, *n* (%)	630/977 (64.4)	720/977 (73.7)	785/977 (80.3)	968/977 (99.1)	977/977 (100)
Cumulative no. of transfused RBC cell units	981	1,052	1,095	1,187	1,192

Primary Outcome

Survival analysis showed lower mortality in transfused patients than in nontransfused patients ($p = 0.005$; **Fig. 3**). On multivariate Cox regression analysis, after adjusting for the propensity of being transfused, RBC transfusion was independently associated with lower 90-day mortality (hazard ratio [HR], 0.55; 95% CI, 0.38–0.79) (**Table 3**). With the exception of mechanical ventilation, time to randomization, presence of nonrenal organ failure and edema, covariates were fairly well balanced across propensity score quartiles (**Supplementary Table 4**, Supplemental Digital Content 1, http://links.lww.com/CCM/B562). Similar independent directional association between RBC transfusion and mortality was found when adjusting for a simplified propensity score (based on hospital characteristics only; **Supplementary Table 5**, Supplemental Digital Content 1, http://links.lww.com/CCM/B562) or without propensity score adjustment (**Supplementary Table 6**, Supplemental Digital Content 1, http://links.lww.com/CCM/B562).

In contrast, higher volume of RBC transfusion was variably associated with lower 90-day mortality (propensity score–adjusted HR, 0.96; 95% CI, 0.92–0.99, $p = 0.04$; **Supplementary Table 7** [Supplemental Digital Content 1, http://links.lww.com/CCM/B562], all covariates-adjusted HR, 0.90; 95% CI, 0.87–0.93; $p < 0.001$; **Supplementary Table 8**, Supplemental Digital Content 1, http://links.lww.com/CCM/B562). In the additional multivariate logistic regression analyses, we found no independent associations of RBC transfusion as a binary (odds ratio [OR], 0.64; 95% CI, 0.45–0.91; $p = 0.013$; **Supplementary Table 9**, Supplemental Digital Content 1, http://links.lww.com/CCM/B562) and as a continuous (OR, 0.93; 95% CI, 0.87–0.99; $p = 0.03$; **Supplementary Table 10**, Supplemental Digital Content 1, http://links.lww.com/CCM/B562) variable. Independent associations between lower hemoglobin level at randomization and increased mortality at 90 days were seen in three of seven analyses.

Secondary Outcomes

In separate multivariate linear regression analyses, transfusion of RBCs during ICU admission (vs no transfusion) was not independently associated with increased RRT-free days ($p = 0.58$), increased mechanical ventilation-free days ($p = 0.35$), ICU-free days ($p = 0.90$), or increased hospital-free days ($p = 0.29$) (**Table 4**). In addition, the volume of RBC transfused in ICU was not associated with these secondary outcomes (**Supplementary Table 11**, Supplemental Digital Content 1, http://links.lww.com/CCM/B562).

Sensitivity Analysis

To perform a sensitivity analysis, we, a priori, decided to restrict further analyses to those 1,169 patients surviving at least 5 days, that is, at a time when the majority (> 80%) of transfused patients had already received RBCs. Baseline characteristics, hemoglobin trajectories, and outcomes stratified by transfusion status for patients surviving at least 5 days are presented in **Supplementary Table 13** (Supplemental Digital Content 1, http://links.lww.com/CCM/B562) and **Supplementary Figure 1** (Supplemental Digital Content 1, http://links.lww.com/CCM/B562). Unadjusted analysis showed lower survival in patients who were transfused during the first 5 days in ICU than in patients who did not receive RBCs during this time period ($p < 0.001$; **Supplementary Fig. 2**, Supplemental Digital Content 1, http://links.lww.com/CCM/B562).

In the multivariate-adjusted regression analyses, however, no association between RBC transfusion during the first 5 days and death at 90 days was observed when transfusion was treated as a binary (HR, 1.29; 95% CI, 0.90–1.85 and OR, 1.07; 95% CI, 0.75–1.54) or as a continuous (HR, 0.96; 95% CI, 0.90–1.02 and OR, 1.00; 95% CI, 1.00–1.00) (**Supplementary Tables 14–17**, Supplemental Digital Content 1, http://links.lww.com/CCM/B562) variable. Stepwise exclusion of patients who died on day 1 to 7 from the analysis confirmed a persistent lack of association between RBC transfusion and mortality beyond exclusion of patients who died before day 3 (**Supplementary Table 21**, Supplemental Digital Content 1, http://links.lww.com/CCM/B562). No independent association between hemoglobin level at randomization and mortality at 90 days was seen in these analyses (Supplementary Tables 14–17, Supplemental Digital Content 1, http://links.lww.com/CCM/B562).

TABLE 2. Baseline Characteristics and Outcomes in All Patients Stratified by RBC Transfusion During ICU Stay

Characteristics	No RBC (*n* = 488)	RBC (*n* = 977)	*p*
Age (yr)	66.0 (14.4)	63.8 (15.1)	0.01
Gender, male (%)	326/488 (66.8)	620/977 (63.5)	0.21
Weight (kg)	82.0 (13.2)	79.9 (12.7)	0.004
Mechanical ventilation (%)	319/487 (65.5)	763/977 (78.1)	< 0.001
Time from ICU admission to randomization (hr)	32.3 (68.3)	61.1 (136)	< 0.001
Acute physiology and chronic health evaluation III score	104.0 (25.7)	101.6 (25.6)	0.08
Severe sepsis at baseline (%)	246/487 (50.5)	477/977 (48.8)	0.54
Presence of edema (%)	186/488 (38.1)	456/977 (46.7)	0.002
Nonoperative admission diagnosis (%)			
Cardiovascular	201/407 (49.4)	333/642 (51.9)	0.01
Genitourinary	107/407 (26.3)	122/642 (19.0)	
Gastrointestinal	32/407 (7.9)	43/642 (6.7)	
Hematology	3/407 (0.7)	19/642 (3.0)	
Metabolic/endocrine	11/407 (2.7)	14/642 (2.2)	
Neurologic	4/407 (1.0)	7/642 (1.1)	
Respiratory	49/407 (12.0)	97/642 (15.1)	
Transplant	0/407 (0.0)	5/642 (0.8)	
Trauma	0/407 (0.0)	2/642 (0.3)	
Operative admission diagnosis (%)			
Cardiovascular	47/81 (58.0)	222/335 (66.3)	0.67
Genitourinary	1/81 (1.2)	3/335 (0.9)	
Gastrointestinal	25/81 (30.9)	73/335 (21.8)	
Neurologic	2/81 (2.5)	5/335 (1.5)	
Respiratory	1/81 (1.2)	7/335 (2.1)	
Transplant	1/81 (1.2)	8/335 (2.4)	
Trauma	4/81 (4.9)	17/335 (5.1)	
Laboratory values			
Hemoglobin (g/L)	111.5 (21.0)	94.2 (16.6)	< 0.001
Platelet count ($\times 10^9$/L)	195.5 (129)	177.6 (131)	0.01
International normalized ratio (%)	1.8 (0.9)	1.7 (1.0)	0.19
Activated partial thromboplastin time (s)	43.8 (18.7)	46.9 (26.3)	0.03
Ca^{2+} (mmol/L)	1.1 (0.3)	1.1 (0.2)	0.64
Urea (mmol/L)	23.7 (12.6)	23.1 (12.5)	0.34
Creatinine (μmol/L)	373.7 (237)	317.0 (189)	< 0.001
Outcomes			
No. of renal replacement therapy–free days	17.8 (11.6)	17.2 (10.0)	0.28
No. of ICU-free days	50.8 (41.2)	47.8 (37.5)	0.17
No. of hospital-free days	36.3 (36.3)	30.0 (31.8)	< 0.001
No. of mechanical ventilatory–free days	48.4 (42.1)	48.9 (37.9)	0.83
Death at day 28 (%)	214/488 (43.9)	338/977 (34.6)	< 0.001
Death at day 90 (%)	228/488 (46.7)	426/976 (43.6)	0.27

Values are expressed as mean (SD) or as *n* (%).

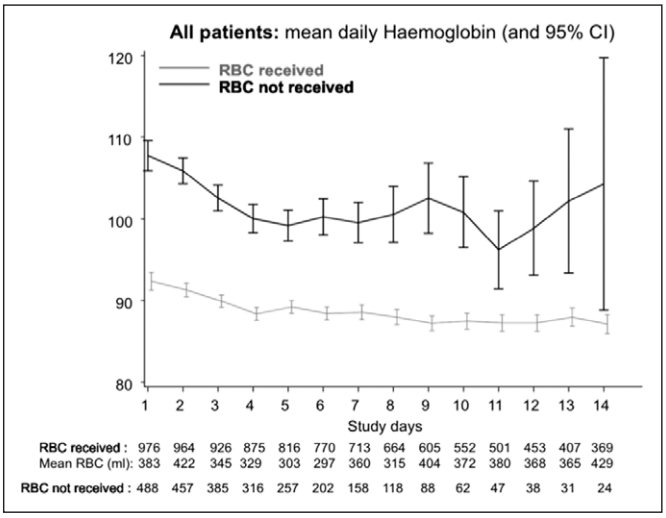

Figure 1. Mean daily hemoglobin levels (in g/L) during the first 2 wk in ICU in patients who did and did not receive RBC transfusion during ICU admission.

On linear regression analysis, patients who survived at least 5 days and who received RBCs during these 5 days spent on average 2.3 days more on RRT ($p = 0.005$) and stayed 8.5 days longer in ICU ($p = 0.007$) than those 5-day survivors who were not transfused during this time-frame (**Supplementary Table 18**, Supplemental Digital Content 1, http://links.lww.com/CCM/B562). There was no independent association between the volume of transfused RBCs and RRT-free days ($p = 0.06$) or ICU-free days ($p = 0.02$; **Supplementary Table 19**, Supplemental Digital Content 1, http://links.lww.com/CCM/B562).

Survival Analysis Using Time-Varying Risk Factors

On multivariate-adjusted time-dependent Cox regression analysis including all patients, we found no robust association between RBC transfusion and 28-day mortality (**Supplementary Table 12**, Supplemental Digital Content 1, http://links.lww.com/CCM/B562). Similar results were obtained after restricting this time-dependent analysis to patients surviving at least 5 days (**Supplementary Table 20**, Supplemental Digital Content 1, http://links.lww.com/CCM/B562).

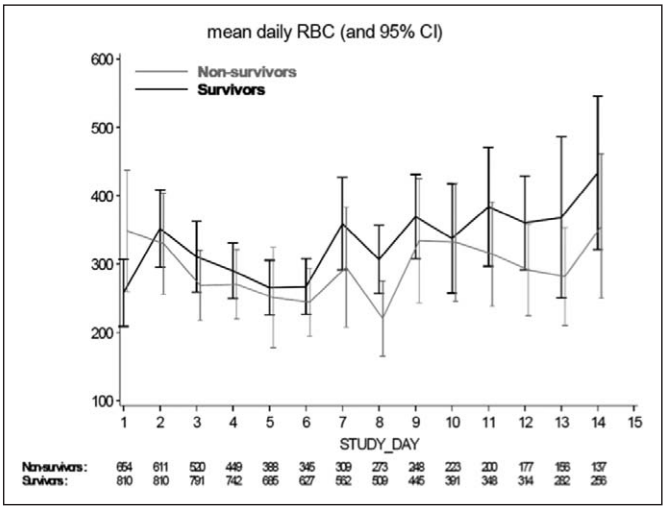

Figure 2. Mean daily volume of RBC transfusion (in mL) during the first 2 wk in ICU according to survival status at 90 d after randomization.

DISCUSSION

Key Findings

Our study investigated the association between RBC transfusion and clinical outcomes in the unique population of critically ill patients with severe AKI treated with CRRT. We found that two thirds of these patients received RBC transfusions during ICU admission. Transfusion with RBC was independently associated with increased survival at 90 days. However, early mortality may have confounded the results because we were unable to demonstrate a persistent independent association between RBC transfusions and mortality when the analyses were restricted to patients surviving at least 5 days. Furthermore, we found no robust independent association between RBC transfusion and other patient-centered outcomes such as RRT-free days, mechanical ventilatory–free days, or length of stay in ICU or hospital. Finally, we found no robust relationship between lower hemoglobin levels at randomization and mortality.

Relation to Previous Studies

In previous studies, approximately 40% of patients received RBC transfusions while in ICU (2–4). The average ICU length of stay (12 d) was, however, greater in the present study, which increased the likelihood of receiving a transfusion and contributed to the much higher proportion of transfused patients. In fact, others have observed comparable proportions, 50–70%, in patients treated in the ICU for more than 7 days.

Another important difference is that we exclusively studied patients with severe AKI treated with CRRT. These patients are particularly prone to anemia for a number of reasons. First, they have impaired erythropoiesis due to a blunted response to erythropoietin (17). Furthermore, a significant proportion of patients may enter the ICU with chronic anemia associated with chronic kidney disease. Information on pre-ICU estimated glomerular filtration rate was available in approximately half of the patients enrolled in the RENAL trial. Of these patients, more than 50% had a baseline estimated glomerular filtration rate below 60 mL/min, suggesting some degree of pre-existing chronic kidney disease (15).

Second, fluid overload with organ edema, a common indication for RRT in general and for randomization into the RENAL trial in particular, may cause hemodilution. The fact that edema was seen in almost half of transfused patients at randomization, significantly more than in nontransfused patients, supports this possibility. In contrast, Nguyen et al (1) found no significant relationship between fluid balance and evolving anemia. However, only the 24-hour fluid balance was considered in that study.

Third, frequent blood sampling may contribute to a low hemoglobin (18). This is particularly important in RRT-treated patients who need close monitoring of electrolytes

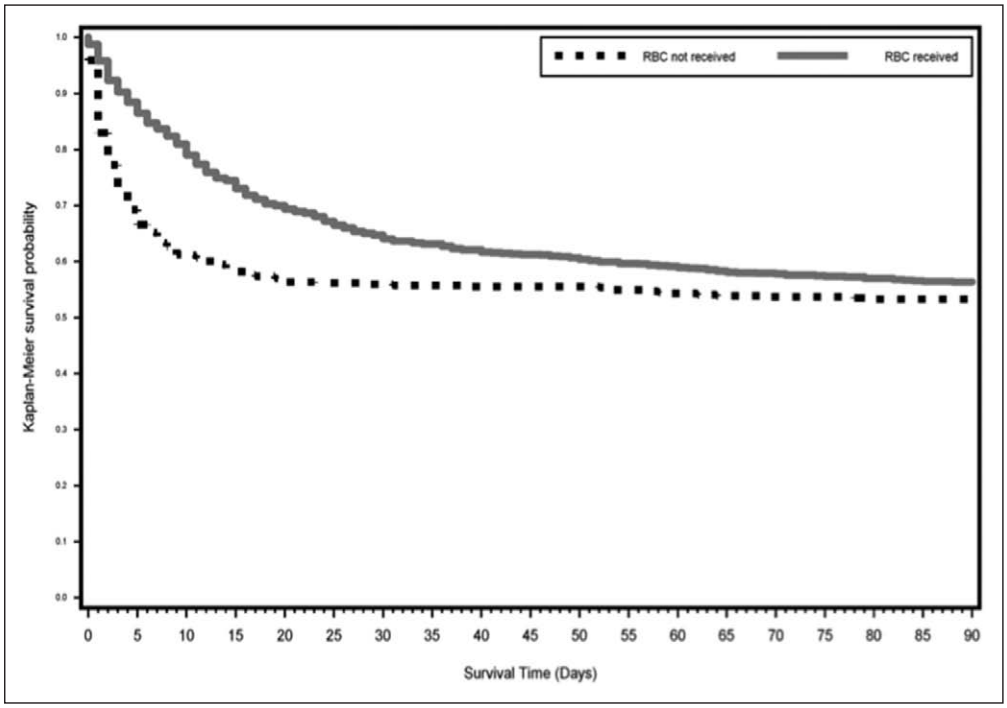

Figure 3. Kaplan-Meier survival graphs from randomization to day 90 comparing all patients who did and did not receive RBC transfusion during ICU admission (log-rank test, $p = 0.005$).

and coagulation parameters. Fourth, blood loss caused by filter clotting and increased risk of bleeding during circuit anticoagulation are well known complications during RRT (19). In the study by Oudemans-van Straaten et al (20) where 200 patients were randomized to regional citrate anticoagulation or nadroparin during CRRT, approximately 60% received RBC transfusions. There was a trend toward more bleeding in the nadroparin group although a similar amount of RBCs were transfused in the two groups. Heparin anticoagulation was used in the majority of RENAL study patients. This might have contributed to bleeding and a high need of RBC transfusions in this cohort.

The hemoglobin concentration decreases with time in critically ill patients (1, 11). Apart from obvious reasons such as bleeding, hemodilution induced by excessive fluid therapy in relation to fluid removal, impaired erythropoiesis, increased destruction of new red cells and frequent blood sampling all contribute to this evolving anemia (21). A decline in hemoglobin of 6.6 g/L/d during the first 3 days in ICU has been shown in nonbleeding patients without hematological disease or renal failure (1). Half that rate was observed in a group of patients with severe AKI of whom 34% received RRT and almost 50% received RBC transfusions (11). In a cohort of more than 2,700 nontransfused critically ill patients, the average decline was 2.8 g/L/d over the first 3–4 days (3). In the present study, initiation of RRT likely fuelled some degree of hemoconcentration when the pre-RRT fluid excess was reversed. This may have blunted the fall in hemoglobin in our patients; only reaching 2.5 g/L/d during the first 3 days in those patients not receiving any RBC transfusions.

TABLE 3. Multivariate Cox Regression Analysis for the Association With 90-Day Mortality Including All Patients

Variable	Adjusted Hazard Ratio[a] (95% CI)	*p*
RBC transfusion in ICU[b] (vs no transfusion)	0.55 (0.38–0.79)	0.001
Mean fluid balance, L	1.42 (1.27–1.58)	< 0.001
Positive mean fluid balance (vs even or negative fluid balance)	1.58 (1.13–2.21)	0.007
Age (yr)	1.02 (1.01–1.03)	0.001

[a]Adjusted for propensity score (based on hospital and patient characteristics) of receiving a RBC transfusion.

[b]Data collected to a maximum of 28 days.

Hazard ratios are presented with 95% CIs. Only variables with $p < 0.01$ in the multivariate analysis presented.

Our observed association between RBC transfusions and increased survival overall stands in contrast to other observational studies and randomized controlled trials. Corwin et al (3) investigated the effect of RBC transfusions on outcomes in more than 4,800 ICU patients. Propensity score–adjusted analysis showed that RBC transfusions were independently associated with an increased risk of death. In addition, the number of transfused units was also associated with longer ICU and hospital length of stay. The apparent beneficial effect of RBC transfusions on survival seen in our study was likely an effect of the competing risk of death; patients who die early are less likely to receive RBCs transfusions. Indeed, this apparent association dissipated when we restricted our analyses to those patients who survived at least 5 days in ICU. Nonetheless, we found no evidence of harm. The fact that our population was exclusively treated with CRRT may explain why RBC transfusions were better tolerated in our study. With CRRT, fluid balance is easily managed, and the potential risk of fluid overload–associated complications (22–26) from transfusions may be attenuated.

Significance of Study Findings

Our study provides the strongest evidence so far that RBC transfusions per se are not associated with adverse patient-centered outcomes in patients treated with CRRT. In addition, it provides

TABLE 4. Multivariate Linear Regression of Secondary Outcomes for All Patients

Variable	Estimates	SEM	*p*
Renal replacement therapy–free days			
RBC transfusion in ICU (vs no transfusion)	0.560	1.005	0.58
Positive mean fluid balance	−4.123	0.877	< 0.001
Time from ICU admission to randomization (d)	−0.016	0.005	< 0.001
Sequential Organ Failure Assessment liver score	−1.632	0.446	< 0.001
APTT (s)	−0.056	0.021	0.008
Mechanical ventilatory–free days			
RBC transfusion in ICU (vs no transfusion)	3.274	3.534	0.35
Positive mean fluid balance	−19.720	3.085	< 0.001
APTT (s)	−0.244	0.074	0.001
ICU-free days			
RBC transfusion in ICU (vs no transfusion)	−0.437	3.463	0.90
Positive mean fluid balance	−20.857	3.043	< 0.001
Time from ICU admission to randomization (d)	−0.046	0.016	0.004
APTT (s)	−0.240	0.071	< 0.001
$Paco_2$ (mm Hg)	−0.369	0.138	0.008
Hospital-free days			
RBC transfusion in ICU (vs no transfusion)	−3.227	3.060	0.29
Positive mean fluid balance	−16.555	2.722	< 0.001

APTT = activated partial thromboplastin time.
Linear estimates are shown with SEM. Transfusion data and variables with $p < 0.01$ in the multivariate analysis are presented.

no consistent evidence that lower hemoglobin concentrations are associated with higher mortality in our analyses. The question of which target hemoglobin is associated with the best outcome is not answered in the present study. In our study, the mean daily hemoglobin in the transfused patients was kept well above the limits defined by previous studies (7–10). Such hemoglobin levels were maintained by transfusion of an average of 300–400 mL of packed RBCs per day. Consequently, we can only comment that, within the boundaries of such practice, the act of transfusing RBCs was consistently not associated with harm. In addition, only leukodepleted blood was used in the RENAL study (27). Another important point to consider is the fact that severe AKI is commonly associated with failure of multiple organs (28) and with a tremendously high mortality (29). Hence these AKI patients are sicker than ICU patients in general and might not tolerate a reduced oxygen delivery, caused by more severe anemia, as well as less acutely ill patients.

Study Strength and Weaknesses

The risk of selection bias in this observational study is acknowledged. First, instead of including all CRRT-treated patients during a given time-frame, patients were selected based on their eligibility into the RENAL trial. Second, we lacked data on premorbid hemoglobin levels and information on the indications for RBC transfusions. Finally, transfusion practice was not standardized across centers involved in the RENAL trial. However, prospectively collected data on daily hemoglobin levels and detailed data on demographics, illness severity and a wide range of biochemical baseline data were used in the multivariate regression models. In addition, we used multiple statistical analyses and considered the competing risk of death.

We did not have transfusion data from the time prior to randomization or after 28 days or ICU discharge. However, because the time between ICU admission and randomization was less than 2 days in the RENAL trial and because the mean study duration was approximately 12 days, the prerandomization period appears unlikely to have affected our findings.

CONCLUSIONS

We found no independent association between RBC transfusion and adverse patient-centered outcomes in a post hoc analysis of the RENAL study patients with severe AKI treated with CRRT. The optimal threshold hemoglobin level for RBC transfusion in CRRT-treated AKI patients needs to be determined in future randomized controlled trials.

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Chapter 16

The Randomized Evaluation of Normal vs. Augmented Level (RENAL) Replacement Therapy Trial

Reflections and Conclusions

This thesis by publication includes 14 peer-reviewed publications leading to and following the largest randomised controlled trial of acute kidney injury treatment. The represent a significant body of knowledge, learning, insights and hypothesis generating observations over close to a decade. When reviewing them to shape a conclusion to the thesis, it is helpful that it is now a little longer than seven years since the publication of **RENAL.** This distance from the pivotal trial has made it possible to have a broader and more reflective view of what its contribution to this field of critical car medicine has been and continues to be. In this regard, some concluding observations can help place this trial and the publications presented in this thesis in a clearer and perhaps more accurate perspective.

To begin with, **RENAL** was a first in several ways: the first study to randomize such a large number of patients with severe AKI; the first to include such a large number of centres in Australia and New Zealand (ANZ); and the first to collect systematic information on so many aspects of treatment in patients with severe AKI.

Its findings have changed practice in ANZ and the world and have been integrated in relevant global consensus statements and guidelines.[1] By demonstrating that higher intensity of CRRT does not improve outcome and by leading to a reduction in CRRT intensity in many units in Australia, RENAL has also led to significant savings, which have more than paid for the cost of its conduct.

The mortality reported for a heterogenous group of patients with severe AKI requiring RRT in ICU in multiple centres was the lowest ever reported in the field and remains the lowest, suggesting that the ANZ approach to severe AKI is of the highest level.

The ability to compare its findings to those of a similar trial in the USA[2] and the observation of a dramatic difference in renal recovery rates, has led to other studies not reported in this thesis, which have focussed on the effect of RRT modality on renal recovery from AKI.[3,4]

The standards set in preparation for **RENAL** (determining by national survey what the standard practice was at the time in order to have a control group that reflects it, describing the screening and enrolment process in detail, and pre-publishing a statistical analysis plan) have now become almost obligatory components of pre-trial activities whenever possible.

The success of RENAL has also made it possible to enable previous investigators from Italy, Switzerland, The Netherlands, Germany and the USA who had done phase II trials in the field[5-9] and investigators from the USA trial of RRT intensity (the ATN trial)[2] to merge their data with those from **RENAL** into a large single database. This recently constituted database will allow important analyses aimed at identifying patient and treatment characteristics which may affect several patient-centred outcomes.

The findings of the **RENAL** sub-study that higher intensity CRRT improved blood pressure and decreased vasopressor therapy contributed to the view that further investigations of higher intensity treatment (so-called high volume hemofiltration) were warranted and led to the design and conduct of the IVOIRE trial of high volume hemofiltration in septic shock.[10]

The notion that RRT is not only about solute control but also about volume control and that such volume control may be just as important if not more important in determining outcome was supported by the additional assessment of fluid balance in **RENAL**. The observation that a more negative fluid balance is strongly and independently associated with better outcomes

spawned several investigations to confirm or refute such findings. Several subsequent studies have indeed confirmed the findings of RENAL[11-13] and have influenced practice toward a more fluid restrictive level of fluid control. Moreover, it has helped provide some of the impetus for ongoing studies of restrictive fluid management in acutely ill patients.

RENAL's focus on hypophosphataemia and the observation of its frequent presence in such critically ill patients rekindled interest in how best to treat this condition, especially when seen in the presence of re-feeding and led to a multicentre phase II randomized controlled trial[14] which revealed that a protocolized approach to caloric restriction in the management of hypophosphatemia increased 90-day survival. A definitive phase III trial is likely to follow.

One of the striking findings of the RENAL trial related to the intake of calories and protein in these very sick patients. The finding that calorie intake was only about 50% of prescribed and therefore half of estimated resting energy expenditure and that protein intake was less than half considered optimal suggested that there is insufficient attention to achieving adequate calorie and protein replacement. These findings and those of others contributed to renewed and systematic interest in resolving these issues by generating definitive evidence. The TARGET program was developed in response to such concerns and, after a promising pilot study,[15] a large 4,000 patients trial is now under way in ANZ to investigate the effect of restoring nutritional intake to prescribed values.

The need to understand the importance of timing of intervention was a major additional focus of the RENAL trial and has contributed in a major way to making a systematic investigation of this issue a priority in critical care nephrology research. Since the findings of the RENAL trial

two important randomized controlled trials of timing have been published[16,17] and a third is underway.[18, 19] The third trial[20] called STARRT for which I am co-investigator and steering and management committee member, is currently recruiting worldwide and if successful, it will exceed RENAL in size and reach with close to 2300 patients randomized. In this way, the journey from RENAL to STARRT has been a logical and continuing evolution of our understanding of the key issues of RRT and, through STARRT, RENAL continues to exert a global impact on critical care nephrology. At the same time, my personal journey has mirrored this evolution in the field of renal replacement therapy and trial medicine and has led to a much deeper understanding of the challenges that must be met in both areas to advance our knowledge, practice and ability to deliver better patient-centred outcomes.

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