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A Precision Medicine Approach to Dosing and Management of Continuous Renal Replacement Therapy for Acute Kidney Injury

Yvelynne P. Kelly MBBChBAO (Hons); MSc.

PhD Candidate in Clinical Medicine

Trinity College Dublin

Student Number 18338253

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Supervisor – Professor Mark Little

Author Statement

I designed, performed the statistical analysis, interpreted the results and wrote the paper for the systematic review and meta-analysis (Chapter 2), the secondary statistical analysis on haemodynamic outcomes (Chapter 3) and the plasma KIM-1 analyses (Chapter 4). 50% of the statistical analysis for the secondary analysis on mechanical ventilation was performed by Dr. Shilpa Sharma (Chapter 5). The AKI-SCAMP trial was designed by Dr. Mallika Mendu (Chapter 6) – I collected the data with the trial coordinator and performed the statistical analysis with the aid of Shimon Shaykevich, biostatistician; then subsequently interpreted the analyses and wrote the resulting paper. I designed, performed and wrote the guidelines for discontinuation of AKI-RRT (Chapter 7) as well as designing, performing and writing the narrative review for vascular access choice in AKI-RRT (Chapter 8).

I have no financial or other conflict of interest to declare.

I declare that this thesis has not been submitted as an exercise for a degree at this or any other university and that it is entirely my own work except where otherwise acknowledged.

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YVELYNNE P. KELLY 2nd January 2021

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CONTENTS

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List of abbreviations

Abbreviation	Meaning
2,3-DPG	2,3-diphosphoglyceric acid
ATN	Acute renal failure Trial Network
ARDS	Acute respiratory distress syndrome
AKI	Acute kidney injury
AKIN	Acute Kidney Injury Network
APACHE	Acute Physiology and Chronic Health Evaluation
AUC	Area under the curve
BFR	Blood flow rate
BUN	Blood urea nitrogen
CAVHDF	Continuous arteriovenous haemodiafiltration
CENTRAL	Cochrane Central Register of Controlled Trials
CPFA	Coupled plasma filtration adsorption
CRRT	Continuous renal replacement therapy
CrCl	Creatinine clearance
CVVH	Continuous venovenous haemofiltration
CVVHD	Continuous venovenous haemodialysis
CVVHDF	Continuous venovenous haemodiafiltration
DBP	Diastolic blood pressure
DFR	Dialysate flow rate
EDD	Extended daily dialysis
EDDF	Extended daily diafiltration
EDTA	Ethylenediaminetetraacetic acid
HD	Haemodialysis
HR	Heart rate
ICU	Intensive care unit
IHD	Intermittent haemodialysis
INR	International normalised ratio
IQR	Interquartile range

KDIGO	Kidney Disease: Improving Global Outcomes
KIM-1	Kidney injury molecule-1
LODS	Logistic organ dysfunction score
MAP	Mean arterial pressure
MICU	Medical intensive care unit
MRI-CEST	Magnetic resonance imaging-chemical exchange saturation transfer
N/A	Not applicable
NTDC	Non-tunnelled dialysis catheter
PA	Pulmonary artery
PMMA	Polymethylmethacrylate
PD	Peritoneal dialysis
P/F	Ratio of arterial oxygen partial pressure to fraction of inspired oxygen
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
RCT	Randomised controlled trial
RevMan	Reviewer Manager software
RFR	Replacement fluid rate
RRT	Renal replacement therapy
SAPS	Simplified Acute Physiology Score
SBP	Systolic blood pressure
SCAMP	Standardised clinical assessment and management plan
SCr	Serum creatinine
SLED	Sustained low efficiency dialysis
SOFA	Sequential organ failure assessment
TDC	Tunnelled dialysis catheter
UO	Urine output
VA	Veterans' Association
VD	Vasopressor dose
VDI	Vasopressor dependency index
VI	Vasopressor index
VIS	Vasopressor inotropic score

Abstract

Background: Despite decades of research, the mainstay of treatment for severe acute kidney injury (AKI) in the critical care setting remains renal replacement therapy in the form of dialysis. Continuous renal replacement therapy (CRRT) poses the risk for unintended adverse events, which in general have been largely under-studied in critical care and nephrology; including depletion of phosphorus, amino acids, catecholamines and trace elements. CRRT also clears the circulation of medications, and dosing guidelines in general are not well established for CRRT.

Aims: Higher intensity CRRT has been studied as a potential therapeutic advance for the treatment of severe AKI by increasing middle molecule clearance, enhancing acid-base buffering and potentially reducing pro-inflammatory cytokines in the setting of sepsis and shock; however it has never been shown to have a mortality benefit. I hypothesised that compared to standard intensity CRRT, higher intensity CRRT leads to greater haemodynamic instability and prolonged mechanical ventilation due to the unregulated removal of small solutes such as phosphate, amino acids, trace elements and medications, and that hypotension on CRRT leads to greater tubular injury, measured with biomarkers specific to ischemic renal tubular injury, and prolonged time to renal recovery. I also assessed the effects of timing of initiation and discontinuation of RRT for AKI on patient outcomes in a randomised controlled trial and performed a systematic review and meta-analysis on the effect of CRRT on hemodynamic instability in critically ill patients.

Methods: I performed secondary statistical analyses of the Acute Renal Failure Trial Network (ATN) trial, which compared intensive versus less intensive RRT dosing for critically ill patients with AKI, during which I assessed the frequency of and risk factors for hypotensive events on CRRT according to treatment dose. I also assessed the effect of intensity of CRRT dosing on time to extubation from mechanical ventilation. I measured plasma KIM-1, a renal-specific biomarker of ischemic tubular injury, in stored blood samples taken from patients during the trial, to assess the ability of plasma renal biomarkers to predict patient outcomes in AKI-RRT. I performed a systematic review and meta-analysis on the effect of CRRT on hemodynamic outcomes in AKI. Finally, I developed evidence-based guidelines for

discontinuation of RRT in the setting of recovery from AKI, as well as performing a narrative review on optimising vascular access for AKI-RRT.

Results: CRRT treatment dose was not a significant risk factor for treatment associated hypotension; nor was ultrafiltration rate. Hypocalcaemia < 1.02 mmol/L was associated with a significantly increased risk of CRRT-associated hypotension. CRRT treatment dose was associated with a significantly longer time to first extubation from mechanical ventilation. Serum phosphate depletion occurred more frequently for patients randomised to higher intensity RRT. For those patients who were successfully extubated initially, there was a significantly higher probability of re-intubation in those randomised to more more-intensive RRT (19% versus 10%; p = 0.03). Plasma KIM-1 was associated with increased risk of 28-day mortality (odds ratio 1.15; 95% CI 1.03-1.29) and decreased likelihood of renal recovery (odds ratio 0.75; 95% CI 0.63-0.9). There was significant heterogeneity present for all outcomes from our meta-analysis of haemodynamic outcomes on CRRT apart from a finding of reduced mean arterial pressure with CVVHD using lactate-buffered dialysate compared to bicarbonate-buffered dialysate. An evaluation of a clinical decision support system for initiation of RRT in the setting of AKI - the Standardized Clinical Assessment and Management Plan (SCAMP) - did not impact the primary outcome of in-hospital, 30-day or 60-day mortality, but did result in a significantly reduced ICU and hospital length of stay for patients with AKI, as well as a reduced 30-day hospital readmission rate. A review of literature including the results of a prospective cohort study performed at Brigham and Women's Hospital in 2017 (Mendu., 2017) showed that tunnelled dialysis catheters (TDC) use is associated with decreased mechanical and infectious complications, as well as improved dialysis delivery by comparison with use of non-tunnelled equivalents.

Conclusions: An individualised approach to CRRT prescribing and management, using evidence-based guidelines, is needed to reduce the risk of adverse events associated with this supportive therapy for severe AKI. In this thesis I have identified modifiable aspects of the CRRT prescription which increase the risk of treatment-associated adverse events. Further dedicated clinical trials will be needed to assess whether optimising these CRRT treatment characteristics improve the risk of adverse outcomes for critically ill patients with AKI.

Lay Abstract

Continuous renal replacement therapy (CRRT) remains the main treatment for patients who suffer from acute kidney failure while severely ill in the intensive care unit (ICU). Though CRRT is the main supportive treatment available that can do the work of the kidneys while they are unable to function appropriately, CRRT can give rise to unintended side-effects due to its continuous nature, which can give rise to excessive removal of important substances such as salts, nutrients, trace elements and medications.

Higher dose CRRT has been studied to assess its benefits in clearing the circulation of harmful substances more quickly and efficiently than CRRT which is prescribed at a lower dose, but has not been shown to reduce the risk of death for those who receive this treatment. I used the Acute Renal Failure Trial Network (ATN) clinical trial dataset and bank of blood samples to assess whether higher dose CRRT increases the risk of harmful low blood pressure for severely ill patients in the ICU, and whether the blood level of kidney injury molecule-1 (KIM-1); a marker secreted by damaged kidney tissue, can help us to predict who is going to recover more quickly from acute kidney failure than others. We have also performed a clinical trial assessing the effect of timing of starting and discontinuing CRRT on outcomes for patients, as well as a systematic review of all available studies that have assessed the effect of CRRT on blood pressure for patients receiving this treatment.

I found that low serum calcium increases the risk of harmful low blood pressure on CRRT, but that the dose of CRRT and the rate at which fluid is removed on CRRT does not affect this. I found that patients on higher dose CRRT tend to require a tube in their airways to support their breathing for significantly longer than patients on conventional dose CRRT. Higher blood levels of KIM-1 were associated with higher risk of death within 28 days and a reduced likelihood of recovering kidney function. Our clinical trial, which assessed the effect of using a form that helps with decision-making about starting and stopping CRRT, did not find an impact on the risk of death but did result in reduced ICU and hospital length of stay, as well as a reduced 30-day readmission rate. My review of the literature demonstrated that using tunnelled dialysis catheters rather than non-tunnelled dialysis catheters is associated with a decreased risk of mechanical and infectious complications, as well as better delivery of dialysis to the patient.

In summary, this thesis shows that there are many modifiable aspects of the CRRT prescription that can significantly affect important outcomes for patients. Dedicated randomised controlled clinical trials will be needed to assess whether use of specific targets for these individual treatment characteristics will significantly improve outcomes for critically ill patients with AKI.

Aims and Hypotheses

The question that this research seeks to answer is:

Do CRRT therapy characteristics lead to increased adverse events for critically ill patients with acute kidney injury requiring renal replacement therapy?

To assess whether my findings are of benefit to patients undergoing CRRT, I posed an additional question:

Does an individualised approach to CRRT dosing and management lead to improved outcomes for critically ill patients with acute kidney injury requiring renal replacement therapy?

In light of these research questions, and the research objectives outlined below, this research aims to identify CRRT therapy characteristics that can lead to adverse events for patients, and to propose novel approaches for minimising such adverse events through personalizing CRRT dosing and management strategies.

Research Objectives

In order to address the research questions outlined above, the following research objectives were identified for this thesis:

RO1: Perform a systematic review and meta-analysis on the effects of CRRT on haemodynamic stability in critically ill patients. This included both prospective cohort studies and randomised controlled trials that compared either different CRRT prescriptions, or CRRT versus another dialytic modality for treatment of severe AKI.

RO2: Perform a secondary statistical analysis of the Acute Renal Failure Trial Network (ATN) trial, in which patients were randomised to RRT at two different intensities, to assess the effect of CRRT-associated treatment factors on haemodynamic stability during the trial.

RO3: Use of day 0 plasma kidney injury molecule-1 (KIM-1) as a sensitive and specific biomarker for ischemic kidney proximal tubular injury to prognosticate mortality and renal recovery for patients in the ATN trial.

RO4: Perform a secondary analysis of the ATN trial to assess the impact of CRRT treatment intensity on time to extubation for patients in the trial.

RO5: Perform a randomised controlled trial of daily use of a Standardised Clinical Assessment and Management Plan (SCAMP), compared to sham, for decision-making regarding AKI, timing of RRT and vascular access for AKI-RRT. The primary outcomes of this trial were in-hospital mortality, 30-day mortality, 1-year mortality, hospital length of stay, ICU length of stay and rate of vascular access-associated complications, according to adherence to SCAMP recommendations.

RO6: Development of evidence-based consensus guidelines for discontinuation of RRT in the setting of AKI recovery, using existing prospective cohort studies and randomized controlled trials.

RO7: Optimising the approach to vascular access choice for AKI-RRT, using current evidence from randomized controlled trials and prospective observational studies of tunnelled versus non-tunnelled dialysis catheter use for AKI.

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Experimental Plan

Systematic Review – Meta Analysis

Effects of CRRT on hemodynamic stability in critically ill patients (**RO1**)

- Different CRRT prescriptions
- CRRT v other modalities

Chapter 2

Acute Renal Failure Trial Network (ATN)

HARVARD MEDICAL SCHOOL

Data: Secondary Analysis - 1
Assess the effect of CRRT-associated treatment factors on hemodynamic stability (**RO2**)

- Patients randomised x 2 RRT intensities

Chapter 3

Biomarker Studies
Analysis of plasma kidney injury molecule (KIM-1) (**RO3**)

- Predict mortality
- Predict renal recovery

Chapter 4

Data: Secondary Analysis – 2

Assess the impact of CRRT treatment intensity on time to patient extubation (**RO4**)

Chapter 5

Perform RCT:
Use of decision-making *Standardised Clinical Assessment and Management Plan* (SCAMP) for AKI (**RO5**)

- Timing of RRT and vascular access for AKI-RRT

Chapter 6

Develop evidence-based consensus guidelines for discontinuation of RRT in an AKI recovery setting (**RO6**)

- Use existing prospective cohort studies and randomized controlled trials

Chapter 7

Review vascular access choice for AKI-RRT (**RO7**)

- Use current RCT evidence and prospective observational studies: tunnelled v. non-tunnelled dialysis catheters

Chapter 8

Value of this Research

This work makes notable contributions to the field of CRRT; particularly by identifying treatment-associated adverse events as well as modifiable aspects of the CRRT prescription that can be altered in order to minimise these adverse events, as well as providing an evidence base for timing of initiation and discontinuation of AKI-RRT, and for clinical decision support system use in a critical care setting.

The **major contribution** of this research is to characterise the distribution of baseline plasma KIM-1 in a cohort of critically ill patients with severe AKI requiring RRT, using microbead assays and Luminex-based methods previously described by our laboratory group. This provides valuable information about the pattern of KIM-1 elevation in this patient population, as well as potentially adding to the clinical applicability of renal proximal tubular biomarkers in prognosticating outcomes and adverse events for patients with AKI requiring RRT. My secondary statistical analysis of the ATN trial to assess the effect of intensity of RRT dosing on time to extubation from mechanical ventilation is also of key importance as a **major contributor** to the literature in this field. The identification of baseline hypophosphatemia as a significant risk factor for prolonged time to extubation, decreased ventilator-free days and increased risk of re-intubation will have a profound impact on future guidelines for dosing and management of CRRT. Another **major contribution** is the completion of an international PROSPERO-registered systematic review and meta-analysis focusing on the effect of CRRT on hemodynamic stability in critically ill patients which will contribute greatly to the existing literature on CRRT-associated adverse events. An additional **major contribution** is the presentation of the results of the SCAMP (Standardised Clinical Assessment and Management Plan) trial; a single centre randomised controlled trial which we designed and carried out at Brigham and Women's Hospital in Boston in order to assess the impact of use of a clinical decision support system for timing of RRT on outcomes for patients with AKI in the ICU. This trial provides high level clinical evidence for the effect of such decision support systems on important outcomes including patient mortality, length of stay, risk of line infections, duration of dialysis treatment and readmission rates.

A **minor contribution** is the development and validation of evidence-based consensus guidelines for discontinuation of RRT in the setting of AKI recovery. Such

guidelines have been significantly lacking to date in the field of AKI management and will provide a useful contribution to clinician decision-making regarding AKI as well as predicting an increased likelihood of successful RRT discontinuation for patients who are managed using these guidelines.

Outputs

To date, three papers directly related to this research have been published:

1. Kelly YP, Waikar SS, Mendu ML. (2019). When to stop renal replacement therapy in anticipation of renal recovery in AKI: the need for consensus guidelines. *Seminars in Dialysis,* **32**(3), 205-209.

This publication proposes a starting framework for RRT discontinuation criteria; synthesising the best-available evidence from clinical trials and observational studies, including receiver-operator curves where applicable, to guide clinicians and clinical researchers

2. Kelly YP, Mendu ML. (2019). Vascular access for renal replacement therapy in acute kidney injury: are non-tunnelled catheters the right choice? *Seminars in Dialysis*, **32**(5), 406-410.

This publication assesses the existing evidence for vascular access choice for AKI requiring RRT and makes the case for increased use of tunnelled dialysis catheters given growing observational evidence for their superiority over non-tunnelled vascular access.

3. Sharma S, Kelly YP, Palevsky PM, Waikar SS - Intensity of renal replacement therapy and duration of mechanical ventilation: secondary analysis of the Acute Renal Failure Trial Network Study. *Chest* May 2020. https://doi.org/10.1016/j.chest.2020.05.542

This is a secondary analysis of the ATN trial dataset in which we assessed the effect of RRT treatment intensity on time to extubation from mechanical ventilation and showed that patients randomised to more intensive RRT had a longer duration of mechanical ventilation and a lower hazard rate of successful extubation compared to those randomised to less intensive RRT; an effect which seems to be mediated by increased rates of hypophosphatemia associated with intensive RRT.

2 conference presentations directly related to this research have also been presented:

1. Kelly YP, Mothi SS, Waikar SS – Potential adverse hemodynamic effects of higher intensity continuous renal replacement therapy.

   - Poster presentation at the International Symposium of Intensive Care and Emergency Medicine, Brussels, March 2019.

   - Abstract published in *Critical Care* 2019 23(Suppl 2); 72.

2. Kelly YP, Sharma S, McCausland FR, Waikar SS – Potential adverse hemodynamic effects of higher-intensity continuous renal replacement therapy.

   - Poster presentation at the American Society of Nephrology Kidney Week, Washington D.C., November 2019.
   - Abstract published in *JASN* 30 (2019); 443.

4 further publications are being prepared at present:

1. Kelly YP, Sharma S, Mothi SS, McCausland FR, Mendu ML, McMahon GM, Waikar SS. Predictors of CRRT-associated hypotension in the ICU.
2. Kelly YP, Zhou D, Mothi SS, McCausland FR, Mendu ML, Sabbisetti V, Leaf DE, Waikar SS. Higher plasma KIM-1 is associated with increased 28-day mortality and decreased renal recovery in patients with AKI requiring renal replacement therapy.
3. Kelly YP, Ahmed S, Shaykevich S, Orav J, Desai S, Leaf DE, Mandel EI, Robinson E, McMahon G, Czarnecki P, Charytan D, Waikar SS, Mendu ML. Block randomised implementation of a decision-making algorithm for renal replacement therapy initiation in acute kidney injury compared to standard care on AKI-related outcomes.
4. Kelly YP, Scott J, Tio MC, Russo DS, Pinto R, Adhikari N, Zgaga L. A systematic review and meta-analysis of the effect of CRRT on hemodynamic outcomes in AKI.

2 conference presentations are due to take place during the American Society of Nephrology Annual Kidney Week in October 2020:

1. Kelly YP, Ahmed S, Leaf DE, Mandel EI, Robinson ES, McMahon GM, Czarnecki PG, Charytan DM, Waikar SS, Mendu ML. Block randomised implementation of a

decision-making algorithm for renal replacement therapy initiation in acute kidney injury compared to standard care on AKI-related outcomes.

2. Kelly YP, McCausland FR, Mendu ML, Sabbisetti V, Leaf DE, Waikar SS. Higher plasma KIM-1 is associated with increased mortality and decreased renal recovery in patients with AKI requiring renal replacement therapy.

CHAPTER 1

Introduction

1.1 Motivation

Continuous renal replacement therapy (CRRT) is frequently used to treat patients with acute kidney injury (AKI) in the critical care setting (Koyner., 2014; Lombardi., 2014). CRRT was initially introduced for the treatment of haemodynamically unstable patients with AKI for whom conventional intermittent dialytic modalities are difficult to administer. The continuous nature of CRRT allows for enhanced removal of middle molecules and solutes with large volumes of distribution and intracellular localisation (Ricci., 2006; Böhler., 1999; Clark., 1999). However, the continuous nature of CRRT also poses the risk for unintended adverse events, which in general have been largely under-studied in critical care nephrology.

Large retrospective cohort ICU studies have shown that up to 43% of patients experience new onset hypotension in the first hour after CRRT initiation (Akhoundi., 2015; Uchino., 2007). Hypotension on CRRT is associated with a higher risk of early mortality and can also lead to early withdrawal of therapy due to treatment intolerance (Silversides., 2014; Shawwa., 2019; Tatum., 2017; Katayama., 2016). It is unclear what causes hypotension on CRRT in the absence of volume removal. Treatment dose may play a key role in determining this due to the effect of faster removal of small and middle molecular weight solutes (Maggiore., 2000). Higher intensity CRRT (> 35 ml/kg/hour) has not been shown to decrease mortality in several randomised controlled trials (VA/NIH Acute Renal Failure Trial Network., 2008; RENAL Replacement Therapy Study Investigators., 2009; Park., 2016). However, it has been associated with adverse effects including hypophosphatemia, essential nutrient loss and removal of important medications including antibiotics (Umber., 2014; Lewis 2014). Amino acid losses during CRRT and other dialytic therapies can lead to negative nitrogen balance and worsen the protein catabolic state in critical illness and AKI (Chua., 2012). Hypophosphatemia during CRRT has been shown to be associated with adverse outcomes including prolonged ventilatory and vasopressor support; though has not been shown to associate with ICU mortality for those affected (Lim., 2017). Antibiotic under-dosing is prevalent on CRRT, particularly in the setting of varying doses of CRRT, differing degrees of residual renal function and recovery and significantly altered pharmacokinetics due to acute kidney injury (Hoff., 2019). Despite these concerns, CRRT is still found to frequently be prescribed at high dose in international surveys; particularly for patients with sepsis and

acidaemia (Clark., 2017; Cottle., 2016., Legrand., 2013., Guo 2017). A recent meta-analysis merged individual patient data from randomised controlled trials comparing high versus standard intensity RRT in intensive care patients with severe AKI and found that higher intensity RRT did not affect mortality but did appear to delay renal recovery, with a longer time to cessation of RRT through 28 days (Wang., 2018).

1.2 Research Methodology

This research addressed the above research questions and objectives by following a number of iterative steps that involved theoretical investigation, experimental design, technical implementation, and quantitative and qualitative evaluation. This section provides an overview of the research methodology followed.

Initially a systematic review and meta-analysis investigating the effect of CRRT on haemodynamic stability was designed and registered with PROSPERO International Prospective Register of Systematic Reviews[1]. The review included randomised controlled trials and prospective observational studies which compared the effects of either CRRT at two different prescriptions, or CRRT versus another dialytic modality, on haemodynamic outcomes for patients with AKI in the ICU. In conjunction with Massachusetts General Hospital Treadwell Library, we designed and implemented a search strategy that allowed us to systemically search bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL)[2], Ovid MEDLINE[3], PubMed[4], EMBASE[5], GrayLit Network[6] and the Cochrane Library[7]. We additionally hand-searched journals, meeting abstracts and reference lists of all primary studies for additional references. Two authors performed blinded abstract screening, full-text screening, quality assessment and data extraction, using the Cochrane Collaboration Risk of Bias and Effective Practice and Organisation of Care Tools (Sterne., 2019; Cochrane Effective Practice and Organisation of Care., 2017). Pooling of statistics was subsequently performed using RevMan Version 5 statistical software (Reviewer Manager., 2014). (RO 1)

[1] https://www.crd.york.ac.uk/PROSPERO/

I then undertook a secondary statistical analysis of the Acute Renal Failure Trial Network (ATN) trial, in which patients were randomised to RRT at two different intensities, to assess the effect of modifiable CRRT-associated treatment factors on haemodynamic stability during the trial. SAS statistical software Version 9.4[8] was used to generate longitudinal mixed effects models to assess the risk of severe hypotension over the 0-28 day study period according to CRRT treatment factors, with a random effect for subjects (RO 2).

Day 0 blood samples from patients in the ATN trial were utilised to measure plasma KIM-1, via microbead assays and a Luminex-based technique that was previously described by our laboratory group (Vaidya., 2008; Sabbisetti., 2014). I was therefore able to assess the distribution of baseline plasma KIM-1 prior to commencement of renal replacement therapy in critically ill patients with severe AKI requiring RRT and was subsequently able to investigate the ability of baseline plasma KIM-1 to predict patient outcomes, including 28-day mortality and renal recovery. In this manner I was able to assess the ability of KIM-1 to predict adverse events on CRRT and to potentially add prognostic value and real-time objective monitoring to CRRT dosage and management (RO 3).

Using SAS statistical software Version 9.4, we performed a secondary statistical analysis of the ATN trial to assess the impact of RRT treatment intensity on time to extubation in the trial. We performed subgroup analyses according to baseline serum phosphate concentrations to investigate for evidence of effect modification due to statistical interaction between treatment assignation and baseline serum phosphate tertiles (RO 4).[2]

We performed a single-centre randomised controlled trial at Brigham and Women's Hospital in Boston using a Standardised Clinical Assessment and Management Plan (SCAMPs) compared to a sham form. We used SAS statistical software Version 9.4 to assess the impact of adherence to a SCAMP clinical decision support system versus sham on ICU length of stay, hospital mortality, timing of RRT and vascular access complications (RO 5).

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[2] https://www.cochranelibrary.com/central/
[3] https://ovidsp.ovid.com/
[4] https://www.ncbi.nlm.nih.gov/pubmed/
[5] https://www.embase.com/login
[6] http://www.greynet.org/
[7] https://www.cochranelibrary.com/
[8] https://odamid.oda.sas.com/

I carried out a narrative review of cut-off criteria for successful discontinuation of RRT in the setting of AKI recovery, using existing evidence from randomised controlled trials and prospective observational studies, including receiver-operator curves where available. I then used this evidence as a framework for building consensus guidelines for discontinuation of AKI-RRT; that could subsequently be validated in prospective datasets (RO 6).

I also carried out a narrative review of vascular access for AKI-RRT in the ICU. Using observational data, I was able to assess the current evidence for choosing tunnelled dialysis catheters as initial vascular access for AKI-RRT, compared to non-tunnelled dialysis catheter use (RO 7).

1.3 Thesis Overview

The remainder of this thesis is organised as follows:

Chapter 2 presents the protocol and results for the systematic review and meta-analysis. The chapter starts with a brief introduction to the topic and our reasons for pursuing this review. It then describes the bibliographic sources utilised and the search strategy that was developed in order to do so. The research questions, types of study to be included, study population, condition of interest, exposure, comparators and outcomes are described. The data extraction and quality assessment criteria used are also discussed, as is the strategy for data synthesis and subgroup analysis. The PRISMA flow diagram and meta-analysis results are then presented in written, tabular and graph format.

Chapter 3 presents the results of the secondary statistical analysis of the ATN trial dataset in which I assessed the effect of modifiable CRRT-associated treatment factors on the risk of severe hypotension during the trial. The chapter begins with a literature review of previous studies focusing on the incidence of adverse events according to CRRT prescription. It then describes the ATN trial protocol and the study population and research methods used to conduct this secondary statistical analysis. Results are presented in the form of frequencies, means and standard deviations, and medians and interquartile ranges where data are non-parametric. Proportional distribution hazards (competing risk) regression models are used to test the risk of severe hypotension according to individual CRRT-associated treatment factors; both as a univariate analysis and as a multivariate analysis with age, sex and illness severity indices, treating death as a competing risk.

Chapter 4 presents the results of the measurement of plasma KIM-1 using day 0 blood samples from participants in the ATN trial. The laboratory methodology is described, as well as the statistics used to present the results of our KIM-1 analysis. Day 0 KIM-1 is initially divided into quartiles to assess for non-linear associations between KIM-1 and patient characteristics. Results are presented in the form of frequencies, means and standard deviations, and medians and interquartile ranges where data are non-parametric. A logistic regression model is used to test the risk of mortality according to log2-transformed D0 KIM-1. To account for the competing risk of death, an inverse probability weighted logistic regression is used to test the odds of renal recovery according to log2-transformed D0 KIM-1. The chapter concludes with a discussion of the future direction for use of KIM-1 as a prognostic biomarker in prescribing CRRT.

Chapter 5 presents the results of our secondary statistical analysis of the ATN dataset in which we assess the effect of CRRT treatment intensity on time to extubation from mechanical ventilation during the trial. The chapter begins with a literature review of hypophosphatemia as an adverse effect of CRRT that can potentially lengthen duration of mechanical ventilation. The statistical methodology used in our secondary analysis of the ATN trial is then described. Results are presented in the form of frequencies, means and standard deviations, and medians and interquartile ranges where data are non-parametric. A zero-inflated Poisson regression model with right censoring of data is used to compare ventilator-free days through Day 14 between treatment arms. Terminal extubation was not counted as an event. We calculated ventilator-free days during the first 14 days of study therapy as the days alive minus days receiving mechanical ventilation after study initiation. If a patient died, the number of ventilator-free days were the number of days between extubation and death. The Kaplan-Meier method is used to estimate survival for both treatment groups and compared time to extubation between groups with the use of 2-sided log rank test. Unadjusted and adjusted hazard ratios and corresponding 2-sided 95% confidence intervals are estimated using the Cox-proportional hazards model. A proportional sub-distribution hazards (competing risk) regression is used to examine the effects of treatment assignment on time to first extubation, treating death as a competing risk. Subgroup analyses are performed according to cause of ICU admission as well as treatment type (CRRT vs IHD) modelled as a time varying covariate. The interaction of

treatment group and subgroup treatment type are tested with use of stratified log-rank tests by treatment type to compare the randomised treatment assignment groups. Model selection is based on prior clinical knowledge.

Chapter 6 presents the results of the SCAMP (Standardised Clinical Assessment and Management Plan) single-centre randomised controlled trial. The chapter begins with a literature review of previous studies that have used SCAMPs and other forms of clinical decision support systems for managing acute and chronic disease. The trial protocol is described, followed by the statistical methodology used in its analysis. Results are presented in the form of frequencies, means and standard deviations, and medians and interquartile ranges where data are non-parametric. A Cox proportional hazards model is used to test the risk of mortality according to SCAMP use versus sham; as well as the risk of mortality according to SCAMP adherence versus non-adherence. A Poisson regression model is used to estimate the effect of the SCAMP vs sham and SCAMP adherence vs non-adherence on ICU and hospital length of stay. The chapter concludes with a discussion of the results and the potential for future integration of clinical decision support systems into optimizing management of RRT for AKI.

Chapter 7 presents a framework for consensus guidelines for discontinuation of RRT in AKI. The chapter begins with a literature review of randomised controlled trials and prospective observational studies that have used differing cut-off criteria for determining timing of cessation of RRT. I then synthesise this data to produce objective, evidence-based guidelines for discontinuation of RRT; by assessing the relative success, sensitivity and specificity of existing criteria.

Chapter 8 is a literature review of the current evidence base for choice of vascular access for AKI-RRT. I synthesise the existing evidence from randomised controlled trials and prospective observational studies, including evidence from the SCAMP trial, to make the case for increased use of tunnelled dialysis catheters as first-line vascular access for AKI-RRT, apart from when selected exclusion criteria are present.

Chapter 9 concludes the thesis with a summary of the key contributions of this research, a discussion of how well the objectives were met and how the research questions were answered, and a discussion of future work that may be carried forward from this thesis.

CHAPTER 2

A Meta-Analysis of Haemodynamic Outcomes on CRRT

2.1 Abstract

Introduction: Our aim was to investigate the effect of CRRT on hemodynamic outcomes in critically ill patients with AKI.

Methods: We performed a systematic review and meta-analysis. Cochrane Central Register of Controlled Trials (CENTRAL), OVID Medline, PubMed, EMBASE, GrayLit Network and the Cochrane Library were searched in January 2019 with additional handsearching of references following full text selection. Eligible studies selected were prospective cohort studies and randomised controlled trials that assessed the effect of CRRT on haemodynamic outcomes either in comparison with other dialytic modalities or CRRT at different prescriptions in critically ill patients with AKI.

Results: We identified 92 unique studies (41 randomized controlled trials and 51 prospective cohort studies) out of 1303 citations. The overall methodological quality was low. Mean arterial pressure was significantly lower throughout the treatment period for patients treated with CVVHD using lactate-buffered dialysate compared to those treated with CVVHD using bicarbonate-buffered dialysate (total mean difference -3.1 mm Hg; 95% CI -5.2 to -0.95; p = 0.005; I^2 = 0%). There was a significantly higher risk of intra-dialytic hypotension for patients on CVVHDF compared to those who received SLED during the study period (total risk ratio 1.22; 95% CI 1.05-1.41; p = 0.008; I^2 = 69%). There was also a significantly higher risk of hypotension for patients on CVVHDF compared to those who received PD during the study period (total risk ratio 2.93; 95% CI 1.57-5.47; p = 0.0007; I^2 = 51%). However, only a maximum of 3 studies could be included in each meta-analysis to produce a pooled effect estimate due to variation in hemodynamic outcomes used; therefore we did not have sufficient power to perform subgroup analyses or meta regression to assess whether differences in baseline characteristics could account for the large amounts of heterogeneity observed.

Conclusions: In summary, our systematic review and meta-analysis showed an increased risk of hypotension with CVVHDF compared to PD and SLED and reduced mean arterial pressure during treatment with CVVHD using lactate-buffered dialysate compared to bicarbonate-buffered dialysate, but no other significant risk of adverse hemodynamic outcomes associated with CRRT at any other prescription. Our conclusions are limited by the

relatively small number of studies that could be pooled for meta-analysis. Large dedicated randomized controlled trials with haemodynamic and other adverse events as primary endpoints of CRRT treatment will be needed to determine the true incidence of hemodynamic adverse events according to CRRT prescription.

2.2 Introduction

Review question: What effect does continuous renal replacement therapy have on haemodynamic stability in patients with acute kidney injury?

2.2.1 Description of the condition

Acute kidney injury (AKI) is defined by an abrupt decrease in kidney function resulting in the retention of urea and other nitrogenous waste products and in the dysregulation of extracellular volume and electrolytes (KDIGO Clinical Practice Guideline for Acute Kidney Injury., 2012). AKI is common, harmful and potentially treatable. The risk of death and need for renal replacement therapy (RRT) increases with increasing stage of AKI (Bagshaw., 2008). AKI complicates 20% of inpatient admissions and is seen at rates as high as 30-50% in the intensive care unit (Star., 1998). The cost of AKI in the United States health system has been estimated at $10 billion dollars per annum (Vandijck et al., 2007). Gallagher et al (2014) found that patients with AKI treated with RRT in the ICU have increased mortality over a 3.5-year follow-up period - overall 31.9% of those surviving to 90 days died during the extended follow-up period. A recent meta-analysis also showed that AKI is associated with a longer length of stay both in the intensive care unit and the hospital (Vandenberghe., 2016). Individuals who survive an AKI hospitalization have a greater likelihood of a recurrent hospital admission compared to those without AKI (Sawhney., 2017) and are at increased risk of developing end stage renal disease (See., 2019).

2.2.2 How the intervention works

Despite decades of research, continuous renal replacement therapy (CRRT) remains the mainstay of treatment for AKI in the critical care setting (Koyner., 2014). Haemodynamic derangement, including hypotension, on CRRT is common. Large retrospective cohort ICU studies have shown that up to 43% of patients experience new onset hypotension in the first hour after CRRT initiation (Akhoundi., 2015). Hypotension frequently leads to cessation of treatment. Patients who have difficulty in tolerating CRRT are more likely to die at an early stage.

At the same time, high dose CRRT has also been promoted as a potential "rescue therapy" for patients with refractory septic shock and has been thought to reduce vasopressor requirement and mortality for those who respond to this (Honore., 2000). The removal of middle molecules, including cytokines and complement, has been thought to contribute to intradialytic hemodynamic improvement (Locatelli., 2000). However, long-term exposure to high dose CRRT increases the risk of drug and antibiotic extraction, as well as making patient care more complicated, increasing costs, decreasing generalised population accessibility and increasing associated procedural risk (Reiter., 2002). Rapid correction of metabolic acidosis resulting from bicarbonate transfer during CRRT can result in therapy-induced metabolic alkalosis (Morimatsu., 2003). This is also associated with adverse haemodynamic consequences as well as reducing ionised calcium concentrations that can lead to potential cardiac arrhythmias and respiratory depression (Gabutti., 2003).

2.2.3 Why it is important to do this review

No systematic review has focused on the impact of CRRT on haemodynamic outcomes; either in cohort studies or as part of a randomised controlled trial comparing different CRRT doses or comparing CRRT to intermittent haemodialysis/hybrid therapies. Previous reviews have instead focused on the effect of CRRT on mortality and on the efficacy of CRRT. This may in part be due to heterogeneity introduced by the variety of haemodynamic outcomes utilised in different CRRT studies, including change in mean arterial pressure, vasopressor dose, vasopressor index and systolic blood pressure; which adds complexity to potential meta-analyses in this area.

The aim of this systematic review was therefore to pool haemodynamic outcomes from eligible individual studies of CRRT to provide an accurate, valid estimate of the effect that CRRT has on haemodynamic stability for critically ill patients, in order to help to design future CRRT dosing algorithms to improve the safety and efficacy of this therapy. Our overarching goal was to enable intensive care physicians and nephrologists who manage CRRT internationally to produce high quality evidence-based guidelines for dosing and recognition/management of treatment-associated complications of CRRT. The results of this systematic review would also be beneficial for society at large given that AKI occurs commonly and is frequently life-threatening for those affected. By synthesising research findings that improve the quality and safety of CRRT, which remains the mainstay of management of AKI for intensive care patients at present, our results would therefore have a broad impact on societal health.

2.3 Protocol

The protocol for this systematic review and meta-analysis was registered with PROSPERO International Prospective Register of Systematic Reviews (Protocol Number CRD42019126206) on 18th March 2019.

2.3.1 Eligibility Criteria

Types of studies

We included randomized controlled trials (RCTs) and prospective cohort studies as these provide the most robust and unbiased measurement of the effect of CRRT on haemodynamic stability. We included studies reported as full text, abstract-only and unpublished data.

Population

Adult patients (> 18 years of age) with acute kidney injury requiring continuous renal replacement therapy.

Acute kidney injury requiring renal replacement therapy can be defined using either KDIGO, AKIN or RIFLE criteria:

- KDIGO/AKIN Stage 3 (SCr to ≥3.0 × baseline, or SCr increase to ≥4.0 mg/dL (354 μmol/L) or initiation of RRT)
- RIFLE Failure, Loss or ESKD stage (Failure: SCr to >3.0 × baseline, or SCr increase to ≥4.0 mg/dL (354 μmol/L; with increase of 0.5 mg/dL or 44 μmol/L) or initiation of RRT; Loss: Complete loss of kidney function for > 4 weeks; ESKD: Complete loss of kidney function for > 3 months).

Cardiovascular and renal physiology differs substantially for children; hence we focused on adult populations for this systematic review. Continuous renal replacement therapy is the mainstay of treatment for haemodynamically unstable patients with AKI in the ICU – hence this is the population on which we specifically focused in order to assess whether CRRT can in fact make haemodynamic outcomes worse for such patients.

Exposure

Continuous renal replacement therapy including:

- Continuous venovenous haemofiltration
- Continuous venovenous haemodiafiltration
- Continuous venovenous haemodialysis.

Continuous renal replacement therapy is the mainstay of treatment for critically ill patients with AKI in the ICU; therefore we wished to assess its quality and safety for such patients by examining its effects on haemodynamic outcomes.

Outcome

Change in haemodynamic parameters including:

- Reduction in mean arterial blood pressure (MAP)
- Increase in vasopressor dose (VD)
- Increase in vasopressor index (VI)
- Reduction in systolic blood pressure (SBP)

We wished to assess whether CRRT affects haemodynamic stability for critically ill patients. Haemodynamic stability can be reported using several valid parameters, including change in mean/systolic arterial pressure or as an increase in vasopressor dose/index. We included studies that reported haemodynamic outcomes in either of these manners as part of our eligibility criteria. Given the variety of parameters that can be used to assess hemodynamic stability in international literature, we did not predetermine cut-off criteria for clinical significance but decided that we would consider undertaking subgroup analyses of studies that used specific cut-off points.

2.3.2 Search Strategy

Electronic searches

We performed a systematic search of bibliographic databases using the below search strategy; including the Cochrane Central Register of Controlled Trials (CENTRAL), OVID Medline, PubMed, EMBASE, GrayLit Network and the Cochrane Library. We also performed hand searching of reference lists and Nephrology and Critical Care meeting abstracts. We searched all databases from their inception to present and posed no restriction on the language of publication.

Searching other resources

We checked reference lists of all primary studies and review articles for additional references.

Key phrases utilized:

1. acute kidney injury

2. (“acute kidney failure*” or “acute kidney failure” or “acute kidney injury*”).ti,ab.

3. 1 or 2

4. exp hemofiltration/

5. (“continuous renal replacement therap*” or CRRT or “continuous venovenous hemodialysis” or hemofiltration* or hemodiafiltration*).ti,ab

6. 4 or 5

7. hypotension/

8. hemodynamics/

9. arterial pressure/

10. blood pressure/

11. (vasopressor* adj(dos* or index*)).ti,ab

12. (hemodynamic* or hypotensi* or "arterial pressure*" or "systolic blood pressure*").ti,ab

13. 7 or 8 or 9 or 10 or 11 or 12

14. 3 and 6 and 13

2.3.3 Data Collection and Analysis

Steps underlying selection of eligible studies

2 review authors (Yvelynne Kelly and Jennifer Scott) independently screened titles and abstracts for inclusion of all potential studies. Studies that were retrospective in nature, that involved paediatric patients or which solely used non-continuous forms of renal replacement therapy were excluded following initial screening. Full-text articles were retrieved for studies that were potentially eligible. We then independently screened full texts and identified studies for inclusion. We also identified and recorded reasons for exclusion of ineligible studies. Any disagreement was resolved through discussion or the involvement of a third author (Sushrut Waikar). Duplicate records were subsequently removed. We recorded the selection process using Covidence screening software and completed a PRISMA flow diagram and a 'Characteristics of excluded studies" table.

Quality assessment and data extraction

We used the Cochrane Collaboration's "Risk of Bias" and Effective Practice and Organisation of Care tools as described in Version 5.1 of the Cochrane Collaboration Handbook to assess for systematic bias in the design and analysis of randomised controlled trials and prospective cohort studies, including generation of sequence allocation, concealment, blinding re intervention and outcome assessment, incomplete outcome data and selective reporting. The presence/degree of bias was identified as low, high or unclear risk. A third author adjudicated any differences between our assessments. Kappa statistics

were used to calculate the percentage agreement between the team members and to discuss/explain reasons for disagreement, with a kappa value of 0.6 or more considered good agreement. The results of our quality assessment were entered into Review Manager 5 to provide summary figures of the risk of bias for each important outcome (across domains) within and between studies.

We used standardized data extraction forms to collect data on the following:

- Study ID
- Author contact details and linked publications
- Confirmation of eligibility for review (or reasons for exclusion)
- Study design
- Study setting
- Date of study completion
- Inclusion/exclusion criteria
- Study duration
- Length of follow-up
- RCT sequence generation
- Allocation sequence concealment
- Blinding
- Sample framework
- Participant number
- Drop outs
- RRT prescription
- Primary and secondary outcomes (including the definition and unit of measurement used for haemodynamic outcomes; with upper and lower limits of normality where appropriate).
- The number of participants allocated to each group
- The number of participants included in analysis for each group
- The sample size for each outcome
- The number of missing participants

- The summary data for each intervention group for those outcomes specified in the protocol
- Study sponsorship.

We independently extracted outcome data from included studies. We noted in the "Characteristics of included studies" table if the outcome of a particular study had been reported in a manner that could not be utilised. Again, disagreements were resolved by consensus or by involving a third person. I transferred data into the Review Manager file. As second author, Jennifer Scott double-checked study characteristics for accuracy against those reported. When the study was published in a language other than English, we sought assistance from a native speaker/translator with content.

2.3.4 Data synthesis

This is a quantitative review that utilised meta-analysis pooling of statistics using RevMan Version 5 statistical software. Each of the studies included in our systematic review was analysed separately with summary statistics calculated for each study. Results from each study were represented as risk ratios with 95% confidence intervals for dichotomous data and mean differences (MD) for continuous data. We used standardised mean differences (SMD) for studies that use different haemodynamic outcome measurement scales. When data were sufficiently homogenous (clinically and statistically), they were summarised in a meta-analysis as pooled risk ratios or mean differences (for dichotomous or continuous data respectively; with a single summary statistic for each study analysed) in a forest plot for the risk of adverse haemodynamic events on CRRT. Studies were excluded from the meta-analysis where an appropriate outcome had not been measured, where there were significant differences in the characteristics of the patients/methods/statistics used in the study (heterogeneity) and where data from the study were not available.

Heterogeneity

Heterogeneity can occur in a systematic review as a result of clinical heterogeneity due to systematic differences in study participants, in interventions used and in outcomes

chosen and how they are measured. Other sources of heterogeneity include methodological heterogeneity as a result of variability in study design and quality, as well as statistical heterogeneity due to systematic differences in statistical methods and analysis, causing greater variation/bias in the reporting of study results than can be expected due to chance alone.

To address the issue of heterogeneity in our systematic review, we examined the forest plot of effect measures for each of the studies analysed. If the confidence intervals for these pooled effect measures did not overlap there was likely to be significant heterogeneity present. We then utilised the chi-squared test for heterogeneity, where a p value < 0.05 indicated that significant heterogeneity exists. In addition to this, we produced an I^2 statistic using RevMan Version 5 software in order to express the degree of heterogeneity that exists across the studies utilised in our meta-analysis. When heterogeneity was high ($I^2 > 50\%$), we presented the final forest plot with the pooled effect in order to illustrate the different treatment effects that existed across the included studies while also acknowledging that an overall pooled effect could not be reliably calculated due to the extent of heterogeneity that existed across the studies used in our meta-analysis.

2.4 Results

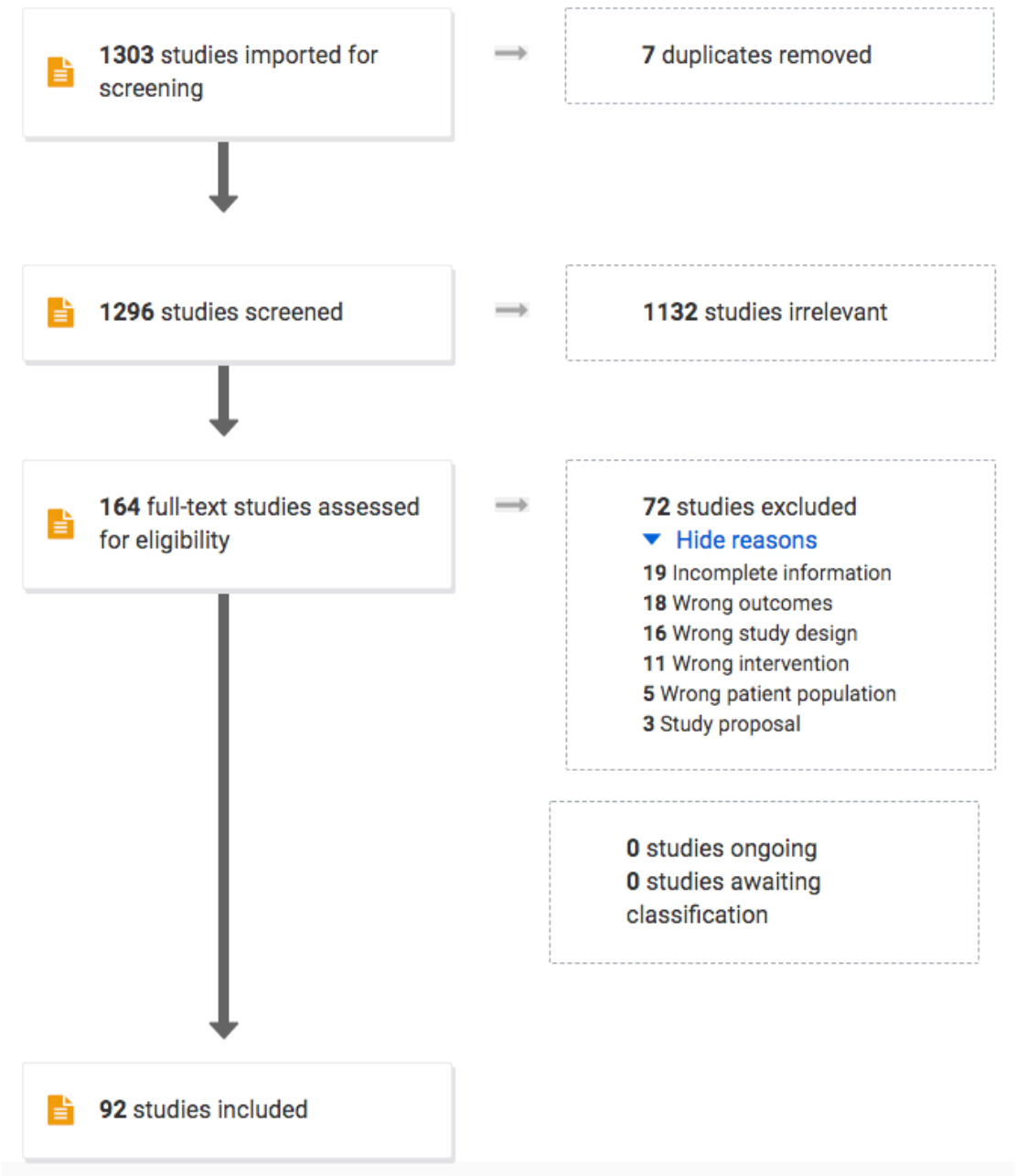
2.4.1 Study Selection

The searches yielded a total of 1303 citations, of which 7 duplicates were removed (MEDLINE 557, Cochrane Library 12, EMBASE 696, GrayLit 0 and handsearching of reference lists 38). 1132 studies were excluded based on title and abstract. 164 studies underwent full text review. Of these, 18 studies were excluded as they studied the wrong outcomes; 19 studies had incomplete information despite multiple attempts made to contact the study authors to provide more information where needed; 16 studies had an incorrect study design; 11 studies had a different intervention; 5 studies used an unrelated patient population and 3 were study proposals instead of completed studies.

In total, 92 studies, including 41 randomised controlled trials and 51 prospective observational studies with a total sample size of 7759 patients, met inclusion criteria (Figure

2.1). Of these, 87 studies were published as articles in peer-reviewed journals and 5 studies were published as abstracts only.

Figure 2.1: PRISMA Flow Diagram



2.4.2 Study Characteristics

All included studies evaluated the effect of CRRT on haemodynamic stability as primary or secondary outcome and had a population sample of adult patients in ICU with AKI requiring RRT. 10 studies compared CRRT with IHD. 8 studies compared CRRT with hybrid modalities including SLED. 64 studies compared 2 or more different CRRT prescriptions or compared use of CRRT in different patient populations. 10 studies compared CRRT either with no RRT, PD or coupled plasma filtration adsorption (CPFA). The studies were performed in 28 countries (the Netherlands, Chile, Germany, Austria, Romania, Italy, France, Greece, the United Kingdom, Belgium, the United States, Canada, China, Egypt, Switzerland, Australia, New Zealand, Israel, Russia, India, Japan, South Korea, Spain, Portugal, Malaysia, Croatia, Saudi Arabia and Cuba). They were published in 7 languages (English, Chinese, Japanese, Korean, Italian, German and French). Official translations were sought for publications that were not published in English. Table 2.1 demonstrates a summary of the characteristics of all included studies.

A variety of different haemodynamic outcome measures were used in these studies; including hypotensive events, epinephrine dose, number of patients on epinephrine, number of patient-days on epinephrine, norepinephrine dose, number of patients on norepinephrine, number of patient-days on norepinephrine, dopamine dose, number of patients on dopamine, number of patient-days on dopamine, dobutamine dose, number of patients on dobutamine, number of patient-days on dobutamine, mean arterial pressure, systolic blood pressure, diastolic blood pressure, intradialytic hypotension, mean pulmonary arterial pressure, pulmonary capillary wedge pressure, right atrial pressure, central venous pressure, cardiac index, cardiac output, heart rate, change in heart rate, change in systolic blood pressure, change in mean arterial pressure, change in pulmonary capillary wedge pressure, change in cardiac output, change in systemic vascular resistance, cardiovascular events, severe hypotension, haemodynamic instability, supraventricular tachycardia, ventricular fibrillation, cardiac arrest, mean decline in MAP on RRT, vasopressor requirement during 1st RRT, increase in vasopressor requirement during 1st RRT, vasopressor dependency index, vasopressor dependency, vasopressin dose, left ventricular ejection fraction, hypotension, intradialytic arrhythmia, arrhythmias, hypotension requiring vasopressor support, hypotension

requiring cessation of RRT, hypotension requiring other intervention, pulmonary vascular resistance, left ventricular stroke work index, pulmonary artery occlusion pressure, pulmonary artery systolic pressure, vasopressor-free days, percentage of total study days on norepinephrine, percentage of total study days on vasopressin, right ventricular ejection fraction, right ventricular end-diastolic volume, right ventricular end-diastolic pressure, increased vasopressor requirement and others. Some haemodynamic outcome measures were specifically defined for the purpose of individual studies; including hypotension, hypotensive events, vasopressor dependency index, vasopressor dependency, inotropic score and modified inotropic score; making it difficult to combine outcome measures due to differences in definition between studies. Some studies also did not define the outcomes which they chose; such as cardiovascular events, hypotensive events, severe hypotension and haemodynamic instability. We were therefore only able to perform a meta-analysis for studies in which both the same interventions and hemodynamic outcome measures were used.

Table 2.1: Characteristics of included studies

Study, Year of Publication	Country	Study Arms	Sample Size	Study Design	Population	Intervention	Outcome Measures
Intermittent vs continuous modalities							
Vinsonneau., 2006	France	IHD	184	Randomised controlled trial	AKI needing RRT with serum creatinine > 310 μmol/L, oliguria < 320 ml/16 hours and multiple organ dysfunction (LODS score ≥ 6).	IHD with bicarbonate-buffered dialysate, BFR 250 ml/min, DFR 500 ml/hour, Nephral 500 or AN69/AN69ST membrane.	Hypotensive events (SBP < 80 mm Hg or fall in SBP > 50 mm Hg below baseline value).
		CVVHDF	175			CVVHDF with bicarbonate-buffered dialysate, BFR 120 ml/min, DFR 500 ml/hour, RFR 1000 ml/hour, AN69 membrane.	
Uehlinger., 2005	Switzerland	IHD	55	Randomised controlled trial	AKI needing RRT with serum creatinine > 350 μmol/L and urine output < 20 ml/hour.	IHD with bicarbonate-buffered dialysate, BFR 150-350 ml/min, DFR 250-1000 ml/hour, polysulfone membrane.	Epinephrine dose; no. of patients on epinephrine; no. of patient-days on epinephrine; norepinephrine dose; no. of patients on

		CVVHDF	70			CVVHDF with bicarbonate-buffered dialysate, BFR 100-180 ml/min, DFR + RFR 1000 ml/hour, AN69 membrane.	norepinephrine; no. of patient-days on norepinephrine; dopamine dose; no. of patients on dopamine; no. of patient-days on dopamine; dobutamine dose; no. of patients on dobutamine; no. of patient days on dobutamine; mean arterial pressure.
Silversides., 2014	Canada	IHD	212	Prospective cohort study	Patients > 16 years old with AKI requiring RRT and for whom fluid balance was available for ≥ 1 day of their ICU admission.	IHD with DFR 500 ml/hour, Xenium membrane.	Intradialytic hypotension (MAP < 65 mm Hg or drop in MAP > 20 mm Hg from starting MAP).
		SLED	61			SLED with DFR 350 ml/hour, Xenium membrane.	
		CVVHDF	219			CVVHDF with DFR + RFR 2000 (1600-3000) ml/hour, Xenium membrane.	
Dai., 2016	China	IHD	38	Prospective cohort study	Patients with sepsis-induced AKI	IHD with BFR 150-200 ml/min,	Cardiovascular events

		CVVHDF	35		requiring RRT (serum creatinine x 2 baseline, > 50% drop in eGFR or urine output < 0.5 ml/kg/hour x > 6 hours).	DFR 500-1000 ml/hour, polysulfone membrane. CVVHDF with BFR 150-200 ml/min, RFR 40 ml/kg/hour, polysulfone membrane.	
Mauritz., 1986	Austria	IHD	22	Prospective cohort study	Patients with pancreatitis or peritonitis and AKI treated with RRT. 17 (85.0)	IHD with acetate-buffered dialysate and CDAK artificial kidney (surface area 1.8 or 2.5 m^2)	Mean arterial pressure; mean pulmonary arterial pressure; pulmonary capillary wedge pressure; right atrial pressure; cardiac index.
		CVVH	27			CVVH with Amicon DS20 and DS30 haemofilters.	
John., 2001	Germany	IHD	10	Randomised controlled trial	18-80 years old with AKI (serum creatinine > 3 mg/dl (265 μmol/L) and/or urine output < 10 ml/hour), septic shock according to	IHD with bicarbonate-buffered dialysate, BFR 250 ml/min, low-flux F6HPS polysulfone membrane.	Change in heart rate; change in systolic blood pressure; norepinephrine dose; change in pulmonary

		CVVH	20		ACCP/SCCM consensus criteria, mechanical ventilation > 48 hours, APACHE II score 20-45, pulmonary capillary wedge pressure 12-18 mm Hg to outrule severe volume overload/deficit and no history of CKD (baseline serum creatinine < 2 mg/dl (177 μmol/L).	CVVH with BFR 250 ml/min, RFR 2000 ml/hour, isotonic acetate-buffered (n = 10) or bicarbonate-buffered replacement fluid (n = 10), AV600 polysulfone membrane.	capillary wedge pressure; change in cardiac output; change in systemic vascular resistance; hypotensive events.
Gašparović., 2003	Croatia	IHD	52	Randomised controlled trial	Patients with AKI in conjunction with multi-organ failure, requiring RRT in the ICU.	IHD with BFR 200-250 ml/min, DFR 500 ml/min, polysulfone membrane.	Hypotensive events (blood pressure drop by 10 mm Hg during RRT).
		CVVH	52			CVVH with RFR 18 ml/kg/hour in the first 33 patients, then 35 ml/kg/hour for the rest, polysulfone membrane.	
Bellomo., 1995[1]	Australia	IHD	40	Prospective cohort study	Patients with sepsis and AKI requiring	IHD with bicarbonate or	Severe hypotension

					RRT in the ICU	acetate-buffered dialysate, BFR 200-300 ml/min, DFR 400-500 ml/min, cuprophane membrane.	
		CVVHDF	87			CVVHDF with 1.5% Dianeal dialysate, BFR 100-150 ml/min, DFR 1000 ml/hour, RFR 1000 ml/hour, AN69S membrane.	
Bellomo., 1995[2]	Australia	IHD/PD	84	Prospective cohort study with retrospective IHD/PD comparator group	Patients with AKI requiring RRT in the ICU	IHD with bicarbonate or acetate-buffered dialysate or PD with 1.5% Dianeal (2 L exchanges), BFR 200-300 ml/min, cuprophane membrane.	Haemodynamic instability; supraventricular tachycardia; ventricular fibrillation; cardiac arrest.
		CVVHDF	150			CVVHDF with 1.5% Dianeal dialysate, BFR 125-150 ml/min, DFR 1000	

						ml/hour, RFR 1000 ml/hour, AN69S membrane.	
Augustine., 2004	United States	IHD	40	Randomised controlled trial	Patients with AKI requiring RRT in the ICU	IHD with bicarbonate-buffered dialysate, BFR 300 ml/min, DFR 500 ml/min, low-flux polysulfone membrane, thrice weekly aiming for weekly Kt/V of 3.6.	Mean arterial pressure; mean decline in MAP on RRT; vasopressor requirement during 1st RRT; increase in vasopressor requirement during 1st RRT.
		CVVHD	40			CVVHD with bicarbonate-buffered dialysate, BFR 200 ml/min, low-flux polysulfone membrane, DFR adjusted to aim for weekly Kt/V of 3.6.	
Hybrid vs continuous modalities							
Schwenger., 2012	Germany	SLED	115	Randomised controlled trial	Patients > 18 years old in the ICU with AKI requiring RRT	SLED with BFR 100-120 ml/min, DFR 120 ml/hour,	Systolic blood pressure; diastolic blood pressure;

		CVVH	117		(with exclusion of post-renal AKI) with either oligoanuria (< 500 ml/24 hours), volume overload, unresponsiveness to fluid resuscitation manoeuvres, serum potassium > 6.5 mmol/L or BUN > 70 mg/dl (25 mmol/L).	high-flux polysulfone membrane. CVVH with BFR 100-120 ml/min, RFR 35 ml/kg/hour, high-flux polysulfone membrane.	hypotensive events.
Kumar., 2004	United States	EDD	26	Randomised controlled trial	Patients in the ICU with AKI requiring RRT. AKI defined as an increase in serum creatinine > 50% baseline value or just prior to hospital admission, with a minimum value > 2 mg/dl (177 μmol/L).	EDD with bicarbonate-buffered dialysate, BFR 200 ml/min, DFR 300 ml/min, polysulfone (F-70) or polymethacrylate (Toray 1.0) membrane.	Mean arterial pressure
		CVVHD	28			CVVHD with BFR 100-200 ml/min, DFR 100-200 ml/min, polysulfone (F-70) or polymethacrylate (Toray 1.0) membrane.	
Shin., 2011	South Korea	SLED	25	Prospective cohort study	Patients in the ICU requiring RRT	SLED with BFR 125-150 ml/min,	Mean arterial pressure;

						DFR 300 ml/min, polysulfone (Fresenius F4 or F6) membrane.	hypotensive events (an acute decrease in SBP < 90 mm Hg).
		CVVHDF	21			CVVHDF with DFR 500-800 ml/hour, RFR 500-1000 ml/hour, AN69 membrane.	
Mishra., 2017	India	SLED	30	Randomised controlled trial	Patients > 18 years old admitted to the ICU with septic shock (defined by the Surviving Sepsis Campaign Guidelines 2012) and AKI (defined by the KDIGO Guidelines 2012).	SLED with BFR 200 ml/min, DFR 250 ml/min, Ultraflux AV600S membrane.	Vasopressor dependency index*; vasopressor dependency**; mean arterial pressure; heart rate.
		CVVH	30			CVVH with BFR 150 ml/min, RFR 30 ml/kg/hour, Ultraflux AV600S membrane.	
Lafuente., 2016	Portugal	SLED	42	Prospective cohort study	Patients with AKI requiring RRT in the ICU	Intervention characteristics not available (poster)	Norepinephrine dose
		CVVH	85				
Kielstein., 2004	Germany	EDD	20	Randomised controlled trial	Patients with oliguric/anuric AKI (urine output < 500 ml/24 hours) requiring respiratory support due to insufficient pulmonary gas	EDD with BFR 200 ml/min, DFR 6000 ml/hour, high-flux polysulfone membrane (F60S).	Norepinephrine dose; mean arterial pressure; heart rate; cardiac output; systemic vascular resistance.

		CVVH	19		exchange.	CVVH with BFR 200 ml/min, RFR 30 ml/kg/hour, high-flux polysulfone membrane (F60S).	
Baldwin., 2007	Australia	EDDF	8	Randomised controlled trial	Patients > 18 yo with AKI by consensus definitions.	EDDF with BFR 100 ml/min, DFR 279 ml/min, RFR 21/min pre filter, polysulfone membrane (Fresenius AV600S).	Heart rate; systolic blood pressure; diastolic blood pressure; mean arterial pressure.
		CVVH	8			CVVH with BFR 200 ml/min, RFR 2000 ml/hour, polysulfone membrane (APS 650).	
Abd Elaziz., 2015	Egypt	SLED	30	Prospective cohort study	Patients with AKI requiring RRT in the ICU.	Intervention characteristics not available (poster)	Change in mean arterial pressure; intradialytic hypotension (> 20% reduction in MAP during dialysis); intradialytic arrhythmia; increased vasopressor
		CVVHDF	30				

Continuous vs continuous modalities							requirement.
Scheenstra., 2012	The Netherlands	CVVH	11	Prospective cohort study	Patients with AKI requiring RRT in the ICU, post haemodynamic stabilisation.	Intervention characteristics not available (poster)	Heart rate
Ruiz., 2010	Chile	High volume CVVH	12	Prospective cohort study	Patients in the ICU with septic shock according to the 1992 ACCP/SCCM consensus criteria, noradrenaline at least 0.3 mcg/kg/min to maintain MAP > 65 mm Hg for at least 1 hour pre CVVH, progressive hyperlactatemia (lactate > 2.4) and an increase during 4 full hours of resuscitation) and a CI of at least 3 L/min/m^2.	High volume CVVH with bicarbonate-buffered replacement fluid, BFR 200 ml/min, RFR 100 ml/kg/hour, polysulfone haemofilter.	Mean arterial pressure; norepinephrine dose; cardiac index; systemic vascular resistance.
Page., 2005	France	CVVHDF	60	Prospective cohort study	Patients in the ICU with AKI, sepsis, refractory circulatory failure and acute lung injury.	CVVHDF with bicarbonate buffered dialysate and replacement fluid, BFR 150 ml/min, DFR 1000 ml/hour, RFR	Heart rate; cardiac index; left ventricular ejection fraction; no. of patients on norepinephrine; no. of patients on

						2000 ml/hour, AN69 polyacrylonitrile membrane.	norepinephrine and dobutamine; no. of patients on epinephrine; vasopressor dose.
Pacher., 1986	Austria	CVVH	8	Prospective cohort study	Patients in the ICU with volume expansion; not mechanically ventilated and not given CPAP. All treated with a dopamine infusion.	CVVH with HF-21 replacement fluid, BFR 150 ml/min, polysulfone Diafilter-30 membrane.	Heart rate; mean arterial pressure; cardiac index; right atrial pressure; mean pulmonary arterial pressure; pulmonary capillary wedge pressure.
Voiculescu., 2003	Romania	CVVHDF	11	Prospective cohort study	Patients in the ICU with AKI requiring RRT +/- other organ dysfunction.	CVVHDF with Soludia 379/Soludia 466/Braun SH 44 Hep dialysate, mean BFR 134 ml/min, mean DFR 35 ml/min, mean RFR 5.6 ml/min, polysulfone BLS membrane.	Hypotension (defined as BP < 85/50 mm Hg).
		CVVH	15			CVVH with Soludia 379/Soludia 466 replacement fluid, mean BFR 117 ml/min, mean	

						RFR 6.4 ml/min, polysulfone HFT 06 or HFT 10 membrane.	
Ratanarat., 2005	Italy	Pulsed high-volume CVVH	12	Prospective cohort study	Patients in the ICU with AKI requiring CRRT and severe sepsis or septic shock (defined by Bone criteria).	Pulsed high-volume CVVH with bicarbonate-buffered replacement fluid (Bi-intensive), BFR 250-300 ml/min, RFR 85 ml/kg/hour x 6 hours followed by 35 m/kg/hour x 18 hours, biocompatible synthetic membrane.	Norepinephrine dose; systolic blood pressure; mean arterial pressure; cardiac index; heart rate.
Morgera., 2004	Germany	CVVH 1 L/hour	6	Randomised controlled trial	Patients with AKI in the course of a septic acute organ failure syndrome. AKI based on at least 1 of the following criteria: fluid overload due to inadequate urine production despite diuretics and maintaining an adequate blood pressure, an	CVVH with bicarbonate-buffered replacement fluid, RFR 1000 ml/hour, polyflux membrane (PS2H).	Mean arterial pressure; central venous pressure; norepinephrine dose.
		CVVH 2.5 L/hour	6			CVVH with bicarbonate-buffered replacement fluid, RFR 2500	

					increase in serum creatinine to > 2.5 mg/dl (221 μmol/L) or doubling of the baseline creatinine value, serum potassium > 5.5 mmol/L due to oligoanuria.	ml/hour, polyflux membrane (PS2H).	
		CVVHD 1 L/hour	6			CVVHD with bicarbonate-buffered dialysate, DFR 1000 ml/hour, polyflux membrane (PS2H).	
		CVVHD 2.5 L/hour	6			CVVHD with bicarbonate-buffered dialysate, DFR 2500 ml/hour, polyflux membrane (PS2H).	
Matamis., 1994	Greece	CVVH	20	Prospective cohort study	Patients in the ICU with septic shock according to Bone criteria and AKI requiring CRRT.	CVVH with Ringer's lactate replacement fluid, mean BFR 157 ml/min, RFR 855 ml/hour, cellulose Amicon-30 membrane.	Mean arterial pressure; mean pulmonary arterial pressure; central venous pressure; pulmonary capillary wedge pressure; heart rate; cardiac output; systemic vascular resistance; pulmonary vascular resistance.

Klouche., 2002	France	CVVH	11	Prospective cohort study	Patients in the ICU with septic shock and AKI (either serum creatinine > 265 umol/L, serum potassium > 5 mmol/L with oliguria < 0.5 ml/kg/hour and/or extracellular volume overload due to oliguria despite high doses of loop diuretics).	CVVH with bicarbonate-buffered replacement fluid, BFR 250 ml/min, RFR 1500-2000 ml/hour, AN69 membrane.	Heart rate; mean arterial pressure; mean pulmonary arterial pressure; right atrial pressure; pulmonary artery occlusion pressure; cardiac index; systemic vascular resistance; pulmonary vascular resistance.
Jones., 1998	United Kingdom	CVVHD with polyacrylonitrile membrane	97	Randomised controlled trial	Patients in the ICU requiring CRRT; not on an ACE-inhibitor.	CVVHD with lactate-buffered dialysate (Hemofiltrasol), BFR 150 ml/min, DFR 35 ml/min, polyacrylonitrile Filtral 10 membrane.	Mean arterial pressure; hypotensive events (defined as those requiring colloids, inotropes or both to resuscitate patients).
		CVVHD with polysulfone membrane	100			CVVHD with lactate-buffered dialysate (Hemofiltrasol), BFR 150 ml/min, DFR 35 ml/min, polysulfone F40	

						membrane.	
Joannes-Boyau., 2004	France	High-volume CVVH	24	Prospective cohort study	Patients > 18 and < 85 years old in the ICU with septic shock according to Bones criteria.	High-volume CVVH with bicarbonate-buffered replacement fluid, BFR 200-300 ml/min, RFR 40-60 ml/kg/hour, polysulfone membrane (Edward Lifesciences)	Systolic blood pressure; cardiac index; systemic vascular resistance; norepinephrine dose.
Joannes-Boyau., 2013	France, Belgium and the Netherlands	High-volume CVVH CVVH	66 71	Randomised controlled trial	Patients > 18 years old in the ICU with septic shock according to the ACCP/SCCM consensus criteria for < 24 hours and AKI fulfilling the criteria for Injury or greater (as per RIFLE criteria) by either serum creatinine or urine output.	High volume CVVH with bicarbonate-buffered replacement fluid (Accusol 35 or Prismasol 4), BFR 200-320 ml/min, RFR 70 ml/kg/hour x 72 hours followed by < 35 ml/kg/hour after that, polyethersulfone membrane (Aquamax). CVVH with bicarbonate-buffered	Mean arterial pressure; systemic vascular resistance; norepinephrine dose; inotropic score***; vasopressor dependency index****.

						replacement fluid (Accusol 35 or Prismasol 4), BFR 200-320 ml/min, RFR 35 ml/kg/hour, polyethersulfone membrane (Aquamax).	
Chung., 2017	United States	CVVH	14	Randomised controlled trial	Adult patients with burns who developed septic shock with AKI at least 2 days post burn. Septic shock defined by the American Burn Association criteria. AKI = oliguria (< 20 ml/hour) x > 24 hours or increase in serum creatinine > 2 mg/dl (177 μmol/L) in men or > 1.5 mg/dl (133 μmol/L) in women over < 4 days.	CVVH with RFR 20-35 ml/kg/hour, NxStage One or Prismaflex hemofilter.	Mean arterial pressure; heart rate; norepinephrine dose; vasopressin dose; modified inotropic score; vasopressor dependency index*****; vasopressor-free days.
		High-volume CVVH	14			High-volume CVVH with RFR 70 ml/kg/hour x 48 hours, then RFR at clinician discretion, NxStage One or Prismaflex hemofilter.	
Zimmerman., 1999	Canada	CVVHD with lactate dialysate	13	Randomised controlled trial (cross-over)	Patients in the ICU with AKI requiring RRT, expected survival > 96 hours and consent from a surrogate.	CVVHD with lactate-buffered dialysate (Dianeal), BFR ≥ 100 ml/min, DFR 1000 ml/hour,	Mean arterial pressure

						AN69 membrane.	
		CVVHD with bicarbonate dialysate	13			CVVHD with bicarbonate-buffered dialysate (Normocarb), BFR ≥ 100 ml/min, DFR 1000 ml/hour, AN69 membrane.	
Zhang., 2012	China	Extra-high volume CVVH	141	Randomised controlled trial	Patients in the ICU > 18 years old with severe sepsis and AKI requiring CRRT. At least one of the following criteria: oliguria (urine output < 100 ml/6 hours and unresponsive to volume resuscitation), K > 6.5 mmol/L, severe acidaemia (pH < 7.2) creatinine > 250 μmol/L or presence of severe organ oedema.	Extra-high volume CVVH with AK-ultra 200 replacement fluid, BFR > 250 ml/min, RFR 85 ml/kg/hour, polysulfone AV600 membrane.	Norepinephrine dose
		High volume CVVH	139			High volume CVVH with AK-ultra 200 replacement fluid, BFR > 250 ml/min, RFR 50 ml/kg/hour, polysulfone AV600 membrane.	

Zayyat., 2018	Egypt	CVVHD	30	Prospective cohort study	Patients in the ICU with haemodynamic instability (MAP < 60 mm Hg and/or requiring vasopressor support before RRT) and AKI requiring RRT. AKI defined by KDIGO 2012 criteria as > 0.3 mg/dl rise in creatinine in 48 hours or > 50% from baseline within 7 days or urine output < 0.5 ml/kg/hour x > 6 hours despite fluid resuscitation.	CVVHD with DFR 35 ml/kg/hour, Fresenius membrane.	Heart rate; systolic blood pressure; diastolic blood pressure; mean arterial pressure; central venous pressure; norepinephrine dose; epinephrine dose; dobutamine dose; left ventricular ejection fraction; pulmonary artery systolic pressure.
Wald., 2012	Canada	CVVH	39	Randomised controlled trial	Patients > 16 years old in the ICU with AKI defined as serum creatinine > 50% above baseline (last premorbid creatinine or earliest value available from current admission). At least 1 of the following indications required for RRT initiation: oliguria (urine output < 100 ml/4 hours),	CVVH with RFR 35 ml/kg/hour (capped at 4000 ml/hour), polyacrylonitrile AN69 membrane.	Percentage of total study days on norepinephrine; percentage of total study days on vasopressin.
		CVVHD	38			CVVHD with DFR 35 ml/kg/hour (capped at 4000 ml/hour), polyacrylonitrile AN69 membrane.	

					metabolic acidosis (HCO3 < 15 and pH < 7.25), refractory hyperkalemia (K > 6.0 despite medical management), urea > 50 mmol/L or suspected uremic organ involvement. Patients had to be haemodynamically unstable with SOFA ≥ 1 on the day of screening.		
Villa., 2014	Italy	High cut-off CVVHD	16	Prospective cohort study	Patients with microbiologically confirmed severe sepsis/septic shock and AKI by RIFLE criteria (at least Failure) requiring RRT within 12 hours of diagnosis.	Intervention characteristics not available (poster)	Vasopressor dependency index
Veenstra., 2014	The Netherlands	CVVH	14	Prospective cohort study	Patients in the ICU with oliguric AKI requiring RRT post hemodynamic stabilisation. Haemodynamic stability defined as positive fluid balance, MAP > 60	CVVH with SH 44 Hep or SH 53 replacement fluid, BFR 200 ml/min, RFR 3000 ml/hour, Nipro-UF 205 membrane.	Heart rate; systolic blood pressure; diastolic blood pressure; mean arterial pressure; norepinephrine dose; central venous pressure.

					mm Hg, central/mixed venous oxygen saturation > 65%, normal lactate and stable/decreased inotropic dosage.		
Uchino., 2007	54 intensive care units in 23 countries	CVVH	1003	Prospective cohort study	Patients > 12 years old admitted to the ICU with AKI requiring CRRT.	CVVH with RFR 20 ml/kg/hour, polyacrylonitrile or polysulfone membrane	Hypotension (> 20% decrease in MAP or an increase in vasopressor requirement within 1 hour of starting CRRT); arrhythmia; cardiac arrest; ventricular fibrillation; supraventricular tachycardia.
Tortorella., 1997	Italy	CVVH	7	Prospective cohort study	Patients in the ICU with AKI and hemodynamic instability requiring CRRT.	CVVH with BFR 200 ml/min, RFR 1500 ml/hour, AN69 polysulfone membrane.	Cardiac index; mean arterial pressure; heart rate.
Thomas., 1997	United Kingdom	Lactate-buffered CVVH	21	Randomised controlled trial	Patients in the ICU who remained acidotic with a base excess > 5 mmol/L	Lactate-buffered CVVH with Haemovex-2 replacement fluid,	Cardiac index; systemic vascular resistance; left ventricular stroke

					following initial resuscitation. Indications for RRT included AKI, control of fluid balance, treatment of severe sepsis or a combination of these indications.	BFR 100 ml/min, RFR 1500-2000 ml/hour, Filtral 12 AN69 polyacrylonitrile membrane. Bicarbonate-buffered CVVH with BFR 100 ml/min, RFR 1500-2000 ml/hour, Filtral 12 AN69 polyacrylonitrile membrane.	work index; dobutamine dose.
		Bicarbonate-buffered CVVH	20				
Sorkine., 1994	Israel	CVVH	9	Prospective cohort study	Patients in the ICU with AKI requiring RRT; all requiring mechanical ventilation.	CVVH with Ringer's Lactate replacement fluid, polyamide membrane (Gambro FH66).	Systolic blood pressure; diastolic blood pressure; heart rate; central venous pressure; pulmonary capillary wedge pressure; cardiac index; systemic vascular resistance.
Parkin., 1994	Australia	CVVHD	10	Prospective cohort study	Patients in the ICU with AKI requiring RRT.	CVVHD with 1.5% Dianeal dialysate, BFR 150 ml/min, DFR 1000 ml/hour, polyacrylonitrile	Right atrial pressure; cardiac output; mean arterial pressure; systemic vascular resistance; mean

						AN69S membrane.	pulmonary arterial pressure; pulmonary capillary wedge pressure.
VA/NIH Acute Renal Failure Trial Network Investigators., 2008	United States	CVVHDF 35 ml/kg/hour or IHD 6 times/week CVVHDF 20 ml/kg/hour or IHD 3 times/week	563 561	Randomised controlled trial	Critically ill adults with AKI consistent with acute tubular necrosis requiring RRT with failure of 1 or more non-renal organ system (non-renal SOFA score ≥ 2) or sepsis. Patients could not have undergone more than 1 IHD/SLED treatment or > 24 hours CRRT pre randomisation.	CVVHDF 35 ml/kg/hour or IHD 6 times/week with cellulose triacetate or synthetic membranes. CVVHDF 20 ml/kg/hour or IHD 3 times/week with cellulose triacetate or synthetic membranes.	Hypotension requiring vasopressor support; hypotension requiring cessation of RRT; hypotension requiring other intervention.
Naumov., 2011	Russia	CVVH	30	Prospective cohort study	Patients with AKI requiring RRT post cardiac surgery.	CVVH with RFR 35 ml/kg/hour.	Mean arterial pressure; cardiac index; dopamine dose; adrenaline dose; dobutamine dose.
Nand., 2010	India	CAVHDF	15	Randomised controlled trial	Patients with AKI who were critically ill (APACHE score > 80) and hemodynamically	CAVHDF with acetate-buffered peritoneal dialysate, alternating	Mean arterial pressure

					unstable with SBP < 90 mm Hg, on invasive ventilator support despite daily hemodialysis.	bicarbonate or calcium based replacement fluid every hours, DFR 1000-1500 ml/hour, cellulose acetate membrane.	
		CVVHDF	15			CVVHDF with acetate-buffered peritoneal dialysate, alternating bicarbonate or calcium based replacement fluid every hours, DFR 1000-1500 ml/hour, cellulose acetate membrane.	
Nakada., 2008	Japan	CVVHDF	43	Prospective cohort study	Patients with de novo septic shock or within 24 hours of ICU admission who were initiated on PMMA-CVVHDF within 24 hours of development of septic shock (defined as per 1992 ACCP/SCCM consensus criteria).	CVVHDF with BFR 80-120 ml/min, DFR 500-1000 ml/hour, RFR 300-500 ml/hour, PMMA membrane (Hemofeel CH-1.0).	Systolic blood pressure; diastolic blood pressure; mean arterial pressure; cardiac index; systemic vascular resistance.

Morgera., 2003	Germany	High-permeability CVVH	16	Randomised controlled trial (crossover)	Critically ill patients with septic shock and AKI. AKI diagnosed when 1 of the following present: fluid overload due to inadequate urine production despite diuretics and maintenance of adequate BP, rise in serum creatinine > 2.5 mg/dl (221 μmol/L) from normal baseline level (or doubling of baseline value), serum potassium > 5.5 mmol/L due to oligoanuria.	High-permeability CVVH with BFR 150 ml/min, RFR 1000 ml/hour, PSH polyamide membrane.	Cardiac output; mean arterial pressure; central venous pressure; norepinephrine dose.
		CVVH	16			CVVH with BFR 150 ml/min, RFR 1000 ml/hour, high-flux Polyflux 11S polyamide membrane.	
McLean., 2000	United Kingdom	CVVHD with lactate-buffered dialysate	54	Randomized controlled trial (crossover)	Patients in the ICU with AKI requiring RRT who completed at least 24 hours on each of the dialysates being studied.	CVVHD with lactate-buffered (Monosol) dialysate, BFR 150-200 ml/min, DFR 1500 ml/hour, polyacrylonitrile Hospal membrane.	Mean arterial pressure

		CVVHD with non-lactate buffered dialysate	54			CVVHD with lactate-free bicarbonate-buffered dialysate (prepared by Baxter), BFR 150-200 ml/min, DFR 1500 ml/hour, polyacrylonitrile Hospal membrane.	
Matsuda., 2010	Japan	CVVHDF with PMMA membrane	32	Prospective cohort study	Patients in the ICU with ARDS and AKI requiring RRT who had not received steroid therapy. AKI diagnosed when all of the following were met: non-responsiveness to water loading and diuretics, BUN > 50 mg/dl and creatinine > 3 mg/dl (265 μmol/L).	CVVHD with PMMA membrane (Hemofeel CH-1.0L), bicarbonate-buffered dialysate (Sublood B), BFR 60-120 ml/min, DFR 500-2000 ml/hour.	Central venous pressure
		IHD + CVVH	19			IHD x 3-4 hours 3-4 times/week with DFR 500 ml/hour, bicarbonate buffered dialysate and regenerated cellulose membrane and CVVH with BFR 60-100 ml/min,	

						polyacrylonitrile or polysulfone membrane.	
Matsuda., 2011	Japan	CVVHDF with polyacrylonitrile membrane CVVHDF with PMMA membrane	13 30	Prospective cohort study	Patients admitted to the ICU with septic shock and AKI within 24 hours of ICU admission. Septic shock defined by the 1992 ACCP-SCCM consensus criteria. AKI defined by serum creatinine > 3.5 mg/dl (310 μmol/L) and urine output < 500 ml/24 hours despite fluid/diuretic administration.	CVVHDF with polyacrylonitrile membrane (Panflo APF-10S), BFR 80-100 ml/min, DFR 500 ml/hour, RFR 300 ml/hour. CVVHDF with PMMA membrane (Filtryzer BK-2.1P), BFR 80-100 ml/min, DFR 500 ml/hour, RFR 300 ml/hour.	Systolic blood pressure; catecholamine index******
Marenzi., 2003	Italy	CVVH	33	Prospective cohort study	Patients in the coronary care unit with oligoanuric AKI post percutaneous coronary intervention with or without overt heart failure.	CVVH with BFR 100-150 ml/min, RFR 1000 ml/hour, Renaflow HF700 hemafilter.	Hypotension
Lobo., 2004	India	CVVHDF	22	Prospective cohort study	Patients with oligoanuric AKI and SBP 100 mm Hg with 2 or more inotropic drugs and 3 or more organ	CVVHDF with peritoneal dialysis dialysate, normal saline/Ringer's lactate replacement fluid,	Hypotensive events

					failures. Failed or technically impossible HD/PD.	BFR 150-175 ml/min, DFR 1000 ml/hour, RFR 1700-2000 ml/hour.	
Langenecker., 1994	Austria	CVVH with heparin	13	Randomised controlled trial	Patients in the ICU with AKI requiring RRT.	CVVH with heparin, polysulfone membrane (Hemofilter D30).	Heart rate; mean arterial pressure; mean pulmonary arterial pressure; systemic vascular resistance; pulmonary vascular resistance; cardiac index.
		CVVH with prostacyclin	14			CVVH with prostacyclin, polysulfone membrane (Hemofilter D30).	
		CVVH with heparin and prostacyclin	19			CVVH with heparin and prostacyclin, polysulfone membrane (Hemofilter D30).	
Heise., 2012	Germany	CVVH	32	Prospective cohort study	Patients > 18 years old requiring CRRT and cardiac monitoring for critical hemodynamic instability whose cause could not be identified. CRRT performed for severe hypervolemia,	CVVH with mean BFR 183 ml/min.	Cardiac output

					hyperkalemia or neurological symptoms due to uraemia.		
Heering., 1997	Germany	CVVH in septic patients	18	Prospective cohort study	Patients in the ICU with AKI due to sepsis (diagnosed according to Bone criteria) or cardiovascular causes; requiring CRRT. AKI diagnosed based on either fluid overload due to inadequate urine production despite diuretics and maintenance of an adequate BP, or a rise in serum creatinine > 265 μmol/Lor serum potassium > 5 mmol/L due to oligoanuria.	CVVH in septic patients with lactate-based replacement fluid (HF03), BFR 150-200 ml/min, RFR 1000 ml/hour, Fresenius AV 600 polysulfone membrane.	Cardiac output; cardiac index; systemic vascular resistance; stroke volume; pulmonary vascular resistance.
		CVVH in non-septic patients	15			CVVH in non-septic patients with lactate-based replacement fluid (HF03), BFR 150-200 ml/min, RFR 1000 ml/hour, Fresenius AV 600 polysulfone membrane.	
Heering., 1999	Germany	Lactate-buffered CVVH	52	Prospective cohort study	Patients with AKI requiring RRT in the ICU. AKI diagnosed based on either fluid overload due to inadequate urine production despite diuretics and	CVVH with lactate-buffered replacement fluid, BFR 150-200 ml/min, RFR 1000 ml/hour, Fresenius AV 600 polysulfone	Cardiac index

					maintenance of an adequate BP, or a	membrane.	
		Acetate-buffered CVVH	32		rise in serum creatinine > 265 μmol/L or serum potassium > 5 mmol/L due to oligoanuria.	CVVH with acetate-buffered replacement fluid, BFR 150-200 ml/min, RFR 1000 ml/hour, Fresenius AV 600 polysulfone membrane.	
		Bicarbonate-buffered CVVH	48			CVVH with bicarbonate-buffered replacement fluid, BFR 150-200 ml/min, RFR 1000 ml/hour, Fresenius AV 600 polysulfone membrane.	
Ganter., 2012	Switzerland	CVVHDF	10	Prospective cohort study	Patients > 18 years old with resuscitated sepsis or signs of inflammation of another origin, persistent volume overload and AKI requiring RRT. Had to be haemodynamically stable, mechanically ventilated and have	CVVHDF with lactate-buffered dialysate and replacement fluid, BFR 100-180 ml/min, DFR 1500 ml/hour, RFR 500 ml/hour, high flux acetonitrile AN69 membrane.	Mean arterial pressure; central venous pressure; cardiac index; pulmonary artery occlusion pressure; heart rate.

					a PA catheter. AKI defined by RIFLE criteria and serum creatinine > 350 μmol/L and/or urine output < 20 ml/hour.		
Forster., 2013	Germany	CVVHD with low-flow CO2 removal	10	Prospective cohort study	Critically ill patients with AKI and hypercapnic respiratory failure requiring mechanical ventilation (pH < 7.25).	CVVHD with low-flow CO2 removal using hollow-fibre gas exchanger, BFR 300-500 ml/min, DFR 1500-4000 ml/hour, high-flux polysulfone membrane (Polyflux 140H).	Mean arterial pressure; heart rate; norepinephrine dose.
Fiaccadori., 2002	Italy	CVVH	51	Prospective cohort study	Patients in the ICU with AKI requiring RRT; indications including severe volume overload, catabolism (daily increase in BUN of 50 mg/dl (18 mmol/L) or more), haemodynamic instability (SBP < 90 mm Hg or need for vasopressors to maintain SBP 90 mm H), intolerance of previous IHD.	CVVH with bicarbonate-buffered replacement fluid (Biosol 20 or 40), BFR 200 ml/min, RFR 1500 ml/hour, polyacrylonitrile, polysulfone, PMMA or ethylvinylalcohol membrane.	Systolic blood pressure; heart rate.

Eastwood., 2012	Australia	CVVH	21	Prospective cohort study (crossover)	A convenience sample of patients in the ICU with AKI requiring CRRT during daytime hours on week-days.	CVVH with increase in BFR by 50 ml/min over 1-4 min to target 200 ml/min, Infomed, Prismaflex or Hygeia membrane.	Change in heart rate; change in central venous pressure; change in norepinephrine dose.
		Slower-start CVVH	21			CVVH with increase in BFR by 20-50 ml/min over 3-10 min to target 200 ml/min, Infomed, Prismaflex or Hygeia membrane.	
Cole., 2001	Australia	High-volume CVVH	11	Randomised controlled trial (crossover)	Septic shock, established oligoanuric AKI due to septic shock, an established need for RRT and a recognised source of sepsis that has been treated and drained surgically where needed.	High-volume CVVH with lactate-buffered replacement fluid, BFR 300 ml/min, RFR 100 ml/min, AN69 membrane. 8 hours of one treatment on 1st day and 8 hours of other treatment of 2nd day (48 hours treatment in total).	Cardiac index; mean arterial pressure; pulmonary artery occlusion pressure; right atrial pressure; norepinephrine dose.

		CVVH	11			CVVH with lactate-buffered replacement fluid, BFR 200 ml/min, RFR 1000 ml/hour, Filtral 12 membrane. 8 hours of one treatment on 1st day and 8 hours of other treatment of 2nd day (48 hours treatment in total).	
Riegel., 1998	Germany	Bicarbonate-buffered CVVH	61	Randomised controlled trial	Patients in the ICU with AKI requiring RRT.	CVVH with bicarbonate-buffered replacement fluid.	Mean arterial pressure
		Lactate-buffered CVVH	56			CVVH with lactate-buffered replacement fluid.	
Morgera., 2006	Germany	High cut-off CVVH	18	Randomised controlled trial	Patients in the ICU with septic shock, AKI and multi-organ failure syndrome. AKI diagnosed based on Acute Dialysis Qualitive Initiative criteria ("failure" or higher based on either	High cut-off CVVH with bicarbonate-buffered replacement fluid, RFR 2500 ml/hour, P2SH high-flux membrane.	Norepinephrine dose
		CVVH				CVVH with	

					eGFR or urine output criteria; whichever was more severe). Septic shock diagnosed based on ACCP/SCCM consensus criteria.	bicarbonate-buffered replacement fluid, RFR 2500 ml/hour, Polyflux 11S high-flux polyamide membrane.	
Macias., 1991	United States	CVVH	10	Prospective cohort study	Patients in the ICU with AKI requiring RRT.	CVVH with 0.9% saline replacement fluid (potassium and bicarbonate added), RFR based on the previous hourly fluid output; including ultrafiltration, Amicon-20 polysulfone membrane.	Hypotensive events
Honoré., 2000	Belgium	Short-term high-volume isovolemic haemofiltration	20	Prospective cohort study	Patients were treated with short-term high-volume isovolemic haemofiltration if the primary hemodynamic end-points of resuscitation were not met: MAP > 55 mm Hg, cardiac index > 2.5 L/min/m^2,	Short-term high-volume isovolemic haemofiltration. BFR 450 ml/min. RFR 8750 ml/min x 4 hours, then 4000 ml/hour. Gambro polysulfone membrane x 4 hours, then AN69	Cardiac index; mean arterial pressure; left ventricular stroke work index; pulmonary artery occlusion pressure; systemic vascular resistance; pulmonary

					max dopamine, dobutamine, noepinephrine, epinephrine doses 0.5 mcg/kg/mn x < 2 hours, PAOP < 16 mm Hg, mixed venous oxygen saturation > 55%, arterial pH > 7.15, serum lactate < 5 mmol/L, PF ratio > 100 with mechanical ventilation	membrane for CVVH.	vascular resistance; epinephrine dose.
Hoffmann., 1996	Germany	CVVH	16	Prospective cohort study	Post-traumatic or post-operative patients admitted to the surgical ICU suffering from severe sepsis and a modified Elebute sepsis severity score > 20.	CVVH with HF 03 replacement fluid, BFR 150 ml/min, RFR 2000 ml/hour, Gambro FH66 polyamide membrane.	Heart rate; central venous pressure; pulmonary artery pressure; pulmonary capillary wedge pressure; cardiac output; cardiac index; left ventricular stroke work index; right ventricular stroke work index; pulmonary vascular resistance; mean arterial pressure; systemic vascular

							resistance; dopamine dose; norepinephrine dose.
Han., 2015	China	Early CVVH	27	Randomized controlled trial	Patients admitted to the ICU who met 1994 American-European Consensus criteria for ARDS.	Early CVVH with bicarbonate-buffered replacement fluid, BFR 150-200 ml/min, Fresenius V600S membrane, commenced within 12 hours of ICU admission.	Central venous pressure; mean arterial pressure; cardiac index.
		Late CVVH	26			Late CVVH with bicarbonate-buffered replacement fluid, BFR 150-200 ml/min, Fresenius V600S membrane, commenced after 48 hours of ICU admission.	
Haase., 2007	Australia	High adsorption CVVH	11	Randomised controlled trial (crossover)	Patients with septic shock and AKI with urine output < 0.5 ml/kg/hour for 2 or more hours (unresponsive to	High adsorption CVVH with lactate-buffered replacement fluid if lactate < 5 (otherwise	Mean arterial pressure; heart rate; central venous pressure; norepinephrine dose.

					fluid resuscitation), serum creatinine > 150 μmol/L if premorbid level normal, rise in creatinine > 80 μmol/L in < 24 hours.	Hemasol used). BFR 180 ml/min, RFR 2000 ml/hour, AN69 polyacrylonitrile membrane changed at 3, 6 and 9 hours.	
		CVVH	11			High adsorption CVVH with lactate-buffered replacement fluid if lactate < 5 (otherwise Hemasol used). BFR 180 ml/min, RFR 2000 ml/hour, AN69 polyacrylonitrile membrane changed every 9 hours.	
Cader Rizna., 2014	Malaysia	CVVH	22	Prospective cohort study	Patients in the ICU with sepsis +/- AKI.	Intervention characteristics not available (poster).	Systolic blood pressure; diastolic blood pressure; mean arterial pressure; heart rate.
Boussekey., 2008	France	CVVH at 35 ml/kg/hour	10	Randomized controlled trial	Patients with septic shock and AKI requiring RRT with at least one of the	CVVH with RFR 35 ml/kg/hour, BFR 180-250 ml/min,	Mean arterial pressure

					following: urine output < 200 ml x 12 hours, serum urea > 30 μmol/L, creatinine > 500 μmol/L or doubling of baseline creatinine for patients with CKD.	bicarbonate-buffered replacement fluid, HF 1400 polyethersulfone membrane.	
		CVVH at 65 ml/kg/hour	9			CVVH with RFR 65 ml/kg/hour, BFR 200-300 ml/min, bicarbonate-buffered replacement fluid, HF 1400 polyethersulfone membrane.	
Biancofiore., 2003	Italy	CVVH with regional anti-coagulation	16	Prospective cohort study	Critically ill patients with AKI requiring RRT – non-obstructive oliguria (< 200 ml/12 hours), severe metabolic acidosis (pH < 7.1), hyperazotemia (BUN > 300 mg/dl or 107 mmol/L), severe coagulopathy requiring large amounts of blood products in patients at risk for pulmonary volumetric over-filling.	CVVH with regional anticoagulation with heparin and protamine, BFR 100-150 ml/min, RFR 1500-1800 ml/hour.	Mean arterial pressure; cardiac index; no. of patients requiring vasopressors or inotropes.
		CVVH with systemic heparin anti-coagulation	11			CVVH with low dose systemic heparin anti-coagulation, BFR 100-150 ml/min, RFR 1500-1800 ml/hour.	

Bellomo., 1994[1]	Australia	CVVHDF	15	Prospective cohort study	Critically ill patients with AKI requiring RRT.	CVVHDF with 1.5% Dianeal dialysate, BFR 150 ml/min, DFR 1000 ml/hour, AN69S membrane.	Dopamine dose; norepinephrine dose; epinephrine dose; heart rate; mean arterial pressure; pulmonary artery occlusion pressure; cardiac index; systemic vascular resistance; mean pulmonary arterial pressure.
Bellomo., 1994[2]	Australia	CVVHD	60	Prospective cohort study	Patients with AKI requiring RRT in ICU.	CVVHD with BFR 125-150 ml/min, DFR 1000 ml/hour, AN69S membrane.	Hypotensive events
Bellomo., 1994[3]	Australia	CVVHD	115	Prospective cohort study	Patients with acute combined respiratory failure and AKI requiring RRT in ICU.	CVVHD with 1.5% Dianeal dialysate, DR 1000 ml/hour, AN69S membrane.	Hypotensive events (defined as decrease in SBP > 20 mm Hg or decrease in MAP > 10 mm Hg).
Bellomo., 1991	Australia	CVVHDF	12	Prospective cohort study	Critically ill patients with AKI requiring RRT in ICU.	CVVHDF with 1.5% Dianeal dialysate, AN69S membrane, DFR 1000 ml/hour.	Change in dopamine dose; change in epinephrine dose; change in

							norepinephrine dose.
Bellomo., 2013	Australia	CVVHDF at 25 ml/kg/hour CVVHDF at 40 ml/kg/hour	59 56	Nested cohort study involving patients from 2 centres of the RENAL trial.	Patients with AKI requiring RRT, critically ill, 18 years or older and either oliguric (urine output < 100 ml/hour x 6 hours) unresponsive to fluid resuscitation, serum potassium > 6.5 mmol/L, severe acidemia (pH < 7.2), BUN > 70 mg/dl (urea > 25 mmol/L), serum creatinine > 3.4 mg/dl (300 μmol/L) or with clinically significant organ oedema.	CVVHDF at 25 ml/kg/hour with BFR > 150 ml/min, AN69 membrane. CVVHDF at 40 ml/kg/hour with BFR > 150 ml/min, AN69 membrane	Change in norepinephrine dose, change in mean arterial pressure.
RENAL Replacement Therapy Study Investigators., 2009	Australia and New Zealand	CVVHDF at 25 ml/kg/hour CVVHDF at 40 ml/kg/hour	741 722	Randomised controlled trial	Patients with AKI requiring RRT, critically ill, 18 years or older and either oliguric (urine output < 100 ml/hour x 6 hours) unresponsive to fluid resuscitation, serum potassium > 6.5 mmol/L, severe acidaemia (pH < 7.2), BUN > 70 mg/dl	CVVHDF at 25 ml/kg/hour with BFR > 150 ml/min, AN69 membrane, Gambro Hemosol B0 dialysate and replacement fluid. CVVHDF at 40 ml/kg/hour with BFR > 150	Arrhythmia; arrhythmia requiring treatment; arrhythmia causing haemodynamic instability.

					(urea > 25 mmol/L), serum creatinine > 3.4 mg/dl (300 μmol/L) or with clinically significant organ oedema.	ml/min, AN69 membrane, Gambro Hemosol B0 dialysate and replacement fluid.	
RENAL Replacement Therapy Study Investigators., 2012	Australia and New Zealand	CVVHDF with a negative mean daily fluid balance	748	Randomised controlled trial	Patients with AKI requiring RRT, critically ill, 18 years or older and either oliguric (urine output < 100 ml/hour x 6 hours) unresponsive to fluid resuscitation, serum potassium > 6.5 mmol/L, severe acidaemia (pH < 7.2), BUN > 70 mg/dl (urea > 25 mmol/L), serum creatinine > 3.4 mg/dl (300 μmol/L) or with clinically significant organ oedema	CVVHDF with a negative mean daily fluid balance, BFR > 150 ml/min, AN69 membrane, Gambro Hemosol B0 dialysate and replacement fluid.	Number of vasopressor days
		CVVHDF with a positive mean daily fluid balance	705			CVVHDF with a positive mean daily fluid balance, BFR > 150 ml/min, AN69 membrane, Gambro Hemosol B0 dialysate and replacement fluid.	
Barenbrock., 2000	Germany	CVVH with bicarbonate replacement fluid	61	Randomised controlled trial	18-80 years old with acute oligoanuric renal failure, azotaemia and/or acute deterioration in renal function associated with volume overload	CVVH with bicarbonate replacement fluid, BFR 200 ml/min, RFR 1000 ml/hour, commercially available hollow-	Systolic blood pressure; diastolic blood pressure; heart rate; central venous pressure; cardiovascular events; number of hypotensive

					refractory to diuretic therapy.	fibre membranes.	events per 24 hours; risk of cardiovascular events.
		CVVH with lactate replacement fluid	56			CVVH with lactate replacement fluid, BFR 200 ml/min, RFR 1000 ml/hour, commercially available hollow-fibre membranes.	
Balgobin., 2018	France	CVVHDF	10	Randomised controlled trial (crossover)	Patients admitted to the ICU with AKI requiring RRT.	CVVHDF with BFR 200 ml/min, DFR 2000 ml/hour, RFR 2000 ml/hour, polysulfone Ultraflux AV1000S membrane.	Intradialytic hypotension (a 20% reduction in MAP or an increase in vasoconstrictive agent dose).
		CVVHD	10			CVVHD with BFR 200 ml/min, DFR 2000 ml/hour, RFR 2000 ml/hour, polysulfone Ultraflux EMiC2 membrane.	
Abdo., 2012	Cuba	CVVHDF in septic patients	11	Prospective cohort study	Patients in the ICU requiring CRRT for > 12 hours for multi-organ failure syndrome.	CVVHDF in septic patients with Hemosol B0 replacement fluid, Dialisan B2GD dialysate, BFR >	Heart rate; mean arterial pressure; norepinephrine dose.

						100 ml/min, DFR 1000 ml/hour, RFR 1000 ml/hour, AN69 membrane.	
		CVVHDF in non-septic patients	7			CVVHDF in non-septic patients with Hemosol B0 replacement fluid, Dialisan B2GD dialysate, BFR > 100 ml/min, DFR 1000 ml/hour, RFR 1000 ml/hour, AN69 membrane.	
Other comparisons							
Siebeck., 2018	Germany	CVVHD	14	Prospective cohort study	Patients in the ICU with KDIGO Stage 3 AKI, indications for RRT and no contra-indication to citrate anti-coagulation.	CVVHD with Ci Ca Dialysate K4 Plus, BFR 100-350 ml/min (set at 3 times DFR), DFR 2000 ml/hour, Ultraflux EMiC2 membrane.	Vasopressor dose; mean arterial pressure; heart rate.
Payen., 2009	France	CVVH	37	Randomised controlled trial	Patients in the ICU with sepsis as per ACCP/SCCM criteria – at least 2 SIRS criteria and 1 sepsis-induced organ failure within 24 hours pre	CVVH with Hemosol B0 bicarbonate-buffered replacement fluid, BFR 150 ml/min,	Number of vasopressor days

					inclusion. SAPS II score 35-63.	RFR 2000 ml/hour, Duraflo II polysulfone membrane.	
		No CVVH	39			Standard of care without CVVH.	
Zhang., 2010	China	CVVH	16	Randomised controlled trial	Patients in the ICU with SIRS complicated by AKI.	CVVH with BFR 180-250 ml/min, RFR 3000-4000 ml/hour, polysulfone AV600 membrane.	Mean arterial pressure
		CVVH + coupled plasma filtration adsorption	14			CVVH + CPFA. BFR 180-250 ml/min, adsorption 100-150 ml/min, plasma separation at 30-40 ml/min, RFR 3000-4000 ml/hour. Polysulfone AV600 membrane. HA330 resin perfusion device with polypropylene P2S 0.5 m plasma separator.	
Meng., 2016	China	CVVH	24	Randomised controlled	Patients in the ICU with onset of septic	CVVH with bicarbonate-	Norepinephrine dose; cardiac

				trial	shock (defined by Surviving Sepsis Campaign Guidelines 2012) and ARDS (defined by the Berlin criteria) within 48 hours.	buffered replacement fluid, BFR 180-220 ml/min, RFR 35 ml/kg/hour, AN69 membrane. Standard of care without CVVH.	index; mean arterial pressure; systemic vascular resistance.
		No CVVH	27				
Combes., 2015	France	High-volume hemofiltration Standard of care (including delayed CVVHDF)	112 112	Randomised controlled trial	Patients post cardiac surgery with persistent shock despite preload optimisation; requiring high-dose catecholamines (epinephrine > 0.2 μg/kg/min, norepinephrine > 0.4 μg/kg/min, epinephrine + [norepinephrine]/2 > 0.2 μg/kg/min, or need for ECMO within 3-24 hours post ICU admission.	High-volume haemofiltration with RFR 80 ml/kg/hour or max 8 L/hour x 48 hours, followed by CVVHDF if needed. DFR 35 ml/kg/hour if CVVHDF subsequently needed. AN69 membrane used. CVVHDF only applied if AKIN Criteria Stage 3 reached. RFR + DFR < 35 ml/kg/hour, AN69 membrane.	Hypotension (defined as introduction of or increase in vasopressors from day 1-30); catecholamine days; catecholamine-free days.
Sanchez-Izquierdo Riera., 1997	Spain	CVVH	15	Randomised controlled trial	Patients in the ICU with traumatic multi-	CVVH with crystalloid replacement fluid,	Mean arterial pressure; pulmonary

					organ dysfunction syndrome (Goris score > 3 for 24-48 hours in total).	BFR 130 ml/min, RFR determined by ultrafiltrate fluid volume; aiming for zero fluid balance, AN69 membrane. Standard of care without CVVH	capillary wedge pressure; central venous pressure; cardiac index; systemic vascular resistance; pulmonary vascular resistance.
		No CVVH	15				
Lentini., 2009	Italy	Pulse high volume haemofiltration Coupled plasma filtration adsorption	8 8	Randomised controlled trial (crossover)	Patients in the ICU with septic shock and AKI; already on CRRT.	Pulse high volume haemofiltration with bicarbonate-buffered replacement fluid, BFR 250-300 ml/min. CVVH used during periods of washout with BFR 150-220 ml/min. RFR 85 ml/kg/hour (35 ml/kg/hour while on CVVH during washout). Polysulfone AV 1000 S or HF1400 membrane used. CPFA with bicarbonate-buffered	Mean arterial pressure; norepinephrine dose; vasopressor score.

						replacement fluid, BFR 200-350 ml/min, RFR 35 ml/kg/hour. Polyethersulfone membrane with sorbent catridge containing a 70 g styrene resin.	
Hassan., 2013	Malaysia	CPFA + CVVH	11	Randomised controlled trial	Patients age 18-75 years old, able to give written informed consent, with severe sepsis/septic shock (according to ACCP/SCCM criteria) with/without AKI.	CPFA + CVVH with BFR 180 ml/min, RFR 35 ml/kg/hour, HF440 CPFA device and Hemofilter DF-140.	Systolic blood pressure; diastolic blood pressure; mean arterial pressure; heart rate.
		CVVH	12			CVVH with BFR 180-200 ml/min, RFR 35 ml/kg/hour, Aquamax membrane.	
George., 2011	India	CVVHDF	25	Randomised controlled trial	Patients in the ICU with multi-organ failure and AKI requiring RRT. AKI defined as a rise in serum creatinine of 0.3 mg/dl (27 μmol/L) or more from baseline or an hourly	CVVHDF with lactated Ringer's replacement fluid, peritoneal dialysis fluid as dialysate. BFR 100-150 ml/min, DFR 1000 ml/hour, Nipro polysulfone	Hypotension

		Continuous PD	25		urine output < 0.5 ml/kg. Indications for RRT were any one or a combination of BUN ≥ 150 mg/dl (54 mmol/L), serum creatinine ≥ 3 mg/dl (265 μmol/L), serum potassium > 6 mmol/L, metabolic acidosis with pH < 7.2, urine output < 0.5 ml/kg x 12 hours despite correction of volume depletion.	haemofilter. Continuous PD with locally available dialysate (additional 25% dextrose added as needed for extra fluid removal). 2 L exchanges (1 L if respiratory distress present), dwell time 30 min.	
Boldt., 1994	Germany	CVVH	15	Prospective cohort study	Patients suffering from AKI (serum creatinine > 3 mg/dl, serum urea > 250 mg/dl, urine output < 20 ml/hour despite intensive diuretic therapy with furosemide) requiring RRT; vs patients with a similar APACHE II score but without AKI.	CVVH with BFR 100-130 ml/min, HF 21 replacement fluid, Fresenius AV 600 membrane. Standard of care without CVVH.	Mean arterial pressure; pulmonary artery pressure; pulmonary capillary wedge pressure; cardiac index; systemic vascular resistance; right ventricular ejection fraction; right ventricular end-diastolic volume; right ventricular end-
		No CVVH	15				

							systolic volume; right atrial pressure; no. of patients on epinephrine; no. of patients on norepinephrine; no. of patients on dopamine.
Al Hwiesh., 2018	Saudi Arabia	CVVHDF Tidal PD	62 63	Randomised controlled trial	Patients with AKI – a rise in serum creatinine > 0.3 mg/dl (27 μmol/L) from baseline or an hourly urine output < 0.5 ml/kg as per the AKIN classification. Indications for RRT were any one or a combination of blood urea ≥ 80 mg/dl (29 mmol/L), serum creatinine ≥ 3 mg/dl (265 μmol/L), serum potassium ≥ 5.5 mmol/L, metabolic acidosis with pH < 7.2 and hourly urine output < 0.5 ml/kg for > 12 hours despite correction of volume depletion.	CVVHDF with Hemosol dialysate, BFR 180-200 ml/min, DFR + RFR 30 ml/kg/hour. Tidal PD with Physioneal 1.36-2.27% (occasionally 3.8% as clinically indicated). 25 L/day. Each fill 2 L with tidal volume 70%. Each PD session lasted 24 hours and sessions were repeated daily.	Hypotension (at least 1 hypotensive episode during RRT – defined as a systolic arterial blood pressure < 90 mm Hg); arrhythmias (defined as supraventricular or ventricular).

BFR: blood flow rate, DFR: dialysate flow rate, RFR: replacement fluid rate, SLED: sustained low efficiency dialysis, EDD: extended daily dialysis, EDDF: extended daily diafiltration, PMMA: polymethylmethacrylate membrane; CPFA: coupled plasma filtration adsorption.
*Vasopressor dependency index defined in Mishra., 2017 as (dopamine dose x 1) + (dobutamine dose x 1) + (adrenaline dose x 100) + (noradrenaline dose x 100) + (phenylephrine dose x 100) + (vasopressin dose x 10).
**Vasopressor dependency defined in Mishra., 2017 as (Vasopressor dependency index/MAP) x 100.
***Inotropic score defined in Joannes-Bayou., 2013 as (dopamine dose x 1) + (dobutamine dose x 1) + (adrenaline dose x 100) + (noradrenaline dose x 100).
****Vasopressor dependency index defined In Joannes-Bayou., 2013 as the ratio of the inotropic score to MAP.
*****Vasopressor dependency index defined in Chung., 2017 as [(dopamine dose x 1) + (dobutamine dose x 1) + (adrenaline dose x 100) + (noradrenaline dose x 100) + (phenylephrine dose x 100) + (vasopressin dose x 10)]/MAP.
******Catecholamine index defined in Matsuda., 2011 as (dopamine dose + dobutamine dose + norepinephrine dose) x 100.

Bellomo., 1995[1] = Bellomo R., Farmer M., Wright C et al. (1995). Treatment of sepsis-associated severe acute renal failure with continuous hemodiafiltration: clinical experience and comparison with conventional dialysis. *Blood Purification*, **13**(5), 246-254.
Bellomo., 1995[2] = Bellomo R., Farmer M., Parkin G. (1995). Severe acute renal failure: a comparison of acute continuous hemodiafiltration and conventional dialytic therapy. *Nephron*, **71**(1), 59-64.
Bellomo., 1994[1] = Bellomo R., McGrath B., Boyce N. Effect of continuous venovenous hemofiltration with dialysis on hormone and catecholamine clearance in critically ill patients with acute renal failure. *Critical Care Medicine*, **22**(5), 833-837.
Bellomo., 1994[2] = Bellomo R., Farmer M., Boyce N. (1994). A prospective study of continuous hemodiafiltration in the management of severe acute renal failure in critically ill surgical patients. *Renal Failure*, **16**(6), 759-766.
Bellomo., 1994[3] = Bellomo R., Farmer M., Boyce N. (1994). Combined acute respiratory and renal failure: management by continuous hemodiafiltration. *Resuscitation*, **28**(2), 123-131.

2.4.3 Risk of bias

Of the 41 included trials, 6 fulfilled all quality indicators (Table 2.2). In terms of selection bias, 6 of the trials were considered to be high risk and 13 unclear risk with regard to sequence generation. 4 of the trials were considered to be high risk and 19 unclear risk with regard to allocation concealment. In terms of detection bias, 2 of the trials were considered to be of unclear risk with regard to blinding of outcome assessment. In terms of attrition bias, 7 of the trials were considered to be high risk and 7 unclear risk with regard to incomplete outcome data. In terms of reporting bias, 1 trial was considered to be high risk and 2 unclear risk with regard to selective outcome reporting. 11 trials were considered to be high risk and 16 unclear risk with regard to other sources of bias.

Of the 51 included prospective cohort studies, only 2 fulfilled all quality indicators (Table 2.3). The intervention was independent of other changes in only 6 studies. The shape of the intervention effect was prespecified in 37 out of 51 studies. The intervention was unlikely to affect data collection in 48 out of 51 studies. Knowledge of the intervention was prevented in 44 out of 51 studies. Full outcome reporting was present in 46 out of 51 studies. Complete outcome data were present in 26 out of 51 studies. The Cohen kappa statistic for inter-rater agreement between reviewers 1 and 2 was 0.7; indicating substantial inter-rater agreement.

Table 2.2: Risk of bias of included trials (using the Cochrane Collaboration Risk of Bias tool)

Study, Year of Publication	Selection bias		Detection bias	Attrition bias	Reporting bias	Other bias
	Random sequence generation (High, Low, Unclear)	Allocation concealment (High, Low, Unclear)	Blinding of outcome assessment (High, Low, Unclear)	Incomplete outcome data (High, Low, Unclear)	Selective reporting (High, Low, Unclear)	Other sources of bias (High, Low, Unclear)
Schwenger., 2012	Low	Low	Low	Low	Low	Low
Payen., 2009	High	High	Low	Low	Low	Unclear
Morgera., 2004	High	Unclear	Low	High	Low	High
Jones., 1998	High	High	Low	Unclear	Low	Unclear
Joannes-Boyau., 2013	Low	Low	Low	Low	Low	High
Chung., 2017	Low	Unclear	Low	Low	Low	High
Zimmerman., 1999	Low	Low	Low	Low	Low	Unclear
Zhang., 2012	Low	Unclear	Low	Low	Low	Unclear
Zhang., 2010	Unclear	Unclear	Low	Unclear	Low	Unclear
Wald., 2012	Low	Low	Low	Low	Low	Low
Vinsonneau., 2006	Low	Low	Low	Low	Low	High
Uehlinger., 2005	Low	Unclear	Low	Low	Low	High

Study, Year of Publication	Selection bias		Detection bias	Attrition bias	Reporting bias	Other bias
	Random sequence generation (High, Low, Unclear)	Allocation concealment (High, Low, Unclear)	Blinding of outcome assessment (High, Low, Unclear)	Incomplete outcome data (High, Low, Unclear)	Selective reporting (High, Low, Unclear)	Other sources of bias (High, Low, Unclear)
Thomas., 1997	Unclear	Unclear	Low	Unclear	Low	Unclear
VA/NIH ATN trial., 2008	Low	Low	Low	Low	Low	Low
Nand., 2010	Unclear	Unclear	Unclear	Low	Low	High
Morgera., 2006	Unclear	Unclear	Low	High	Low	Low
Meng., 2016	Unclear	Unclear	Low	High	Low	Low
Langenecker., 1994	Unclear	Unclear	Low	High	Low	Unclear
Kumar., 2004	High	Unclear	Low	Low	Low	High
Combes., 2015	Low	Unclear	Low	Low	Low	Low
Cole., 2001	Low	Low	Low	Low	Low	Unclear
Sanchez-Izquierdo Riera., 1997	Low	Low	Low	Low	Low	Unclear
Riegel., 1998	Unclear	Unclear	Low	Unclear	Unclear	Unclear
Morgera., 2003	Low	Low	Low	Low	Low	High
Mishra., 2017	Low	Unclear	Low	Low	Low	Low
Lentini., 2009	Low	Low	Low	Low	Low	Unclear

Study, Year of Publication	Selection bias		Detection bias	Attrition bias	Reporting bias	Other bias
	Random sequence generation (High, Low, Unclear)	Allocation concealment (High, Low, Unclear)	Blinding of outcome assessment (High, Low, Unclear)	Incomplete outcome data (High, Low, Unclear)	Selective reporting (High, Low, Unclear)	Other sources of bias (High, Low, Unclear)
Kielstein., 2004	High	High	Low	Low	Low	Low
John., 2001	Unclear	Unclear	Low	Unclear	Low	Unclear
Hassan., 2013	Low	Low	Low	High	Low	High
Han., 2015	Unclear	Unclear	Low	Unclear	Low	Low
Haase., 2007	Low	Low	Low	High	Low	Unclear
George., 2011	Unclear	Unclear	Low	High	Low	High
Gašparović., 2003	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Boussekey., 2008	High	High	Low	Low	Low	Unclear
RENAL trial., 2009	Low	Low	Low	Low	Low	Low
Bellomo., 2013	Low	Low	Low	Low	Low	Low
Barenbrock., 2000	Low	Low	Low	Low	Low	Low
Balgobin., 2018	Low	Low	Low	Low	Low	High
Baldwin., 2007	Unclear	Unclear	Low	Low	Low	Unclear
Augustine., 2004	Unclear	Low	Low	Unclear	Low	Low

Study, Year of Publication	Selection bias		Detection bias	Attrition bias	Reporting bias	Other bias
	Random sequence generation (High, Low, Unclear)	Allocation concealment (High, Low, Unclear)	Blinding of outcome assessment (High, Low, Unclear)	Incomplete outcome data (High, Low, Unclear)	Selective reporting (High, Low, Unclear)	Other sources of bias (High, Low, Unclear)
Al Hwiesh., 2018	Low	Low	Low	Low	High	Low

Table 2.3: Risk of bias of included prospective cohort studies (using the Cochrane Effective Practice and Organisation of Care checklist)

Study, Year of Pub.	Other bias (High/Low/ Unclear)	Intervention independent of other changes (High, Low, Unclear)	Shape of intervention effect prespecified (High, Low, Unclear)	Intervention unlikely to affect data collection (High, Low, Unclear)	Knowledge of interventions prevented during the study	Selective reporting (High, Low, Unclear)	Incomplete outcome data (High, Low, Unclear)
Scheenstra., 2012	High	Unclear	Low	Low	Low	Low	High
Ruiz., 2010	High	High	High	Low	Low	Low	Low
Page., 2005	Unclear	Unclear	Low	Low	Low	Low	Low
Pacher., 1986	High	Unclear	Low	Low	Low	Low	Low
Voiculescu., 2003	High	Unclear	Unclear	Low	Unclear	Low	Low
Ratanarat., 2005	High	High	Low	Low	Low	Low	Low
Matamis., 1994	High	Unclear	Low	Low	Low	Low	Low
Klouche., 2002	High	Unclear	Low	Low	Low	Low	Low
Joannes-Boyau., 2004	High	Unclear	Low	Low	Low	Low	High
Zayyat., 2018	Unclear	Unclear	Low	Low	Low	Low	Low
Villa., 2014	High	Unclear	Low	Low	Low	Low	Unclear
Veenstra., 2014	High	Unclear	Low	Low	Low	Low	High

Study, Year of Pub.	Other bias (High/Low/ Unclear)	Intervention independent of other changes (High, Low, Unclear)	Shape of intervention effect prespecified (High, Low, Unclear)	Intervention unlikely to affect data collection (High, Low, Unclear)	Knowledge of interventions prevented during the study	Selective reporting (High, Low, Unclear)	Incomplete outcome data (High, Low, Unclear)
Uchino., 2007	High	Low	Low	Low	Low	Low	Low
Tortorella., 1997	High	High	Unclear	Low	Unclear	Unclear	Unclear
Sorkine., 1994	High	Unclear	Low	Low	Low	Low	Unclear
Silversides., 2014	Low	Low	Low	Low	Low	Low	Low
Parkin., 1994	High	Unclear	Low	Low	Low	Low	Low
Naumov., 2011	High	Unclear	Low	Low	Low	Unclear	Unclear
Nakada., 2008	Unclear	Unclear	Low	Low	Low	Low	Unclear
McLean., 2000	Low	Low	Low	Low	Low	Low	Low
Matsuda., 2010	High	Low	Low	Low	Low	Low	Low
Matsuda., 2011	Unclear	High	Low	Low	Low	Low	Low
Marenzi., 2003	High	Unclear	Low	Low	Unclear	Low	Low
Lobo., 2004	High	Unclear	Unclear	Low	Unclear	Low	Low
Heise., 2012	High	High	Low	High	Low	Low	High
Heering., 1997	High	Unclear	Low	Low	Low	Low	Unclear

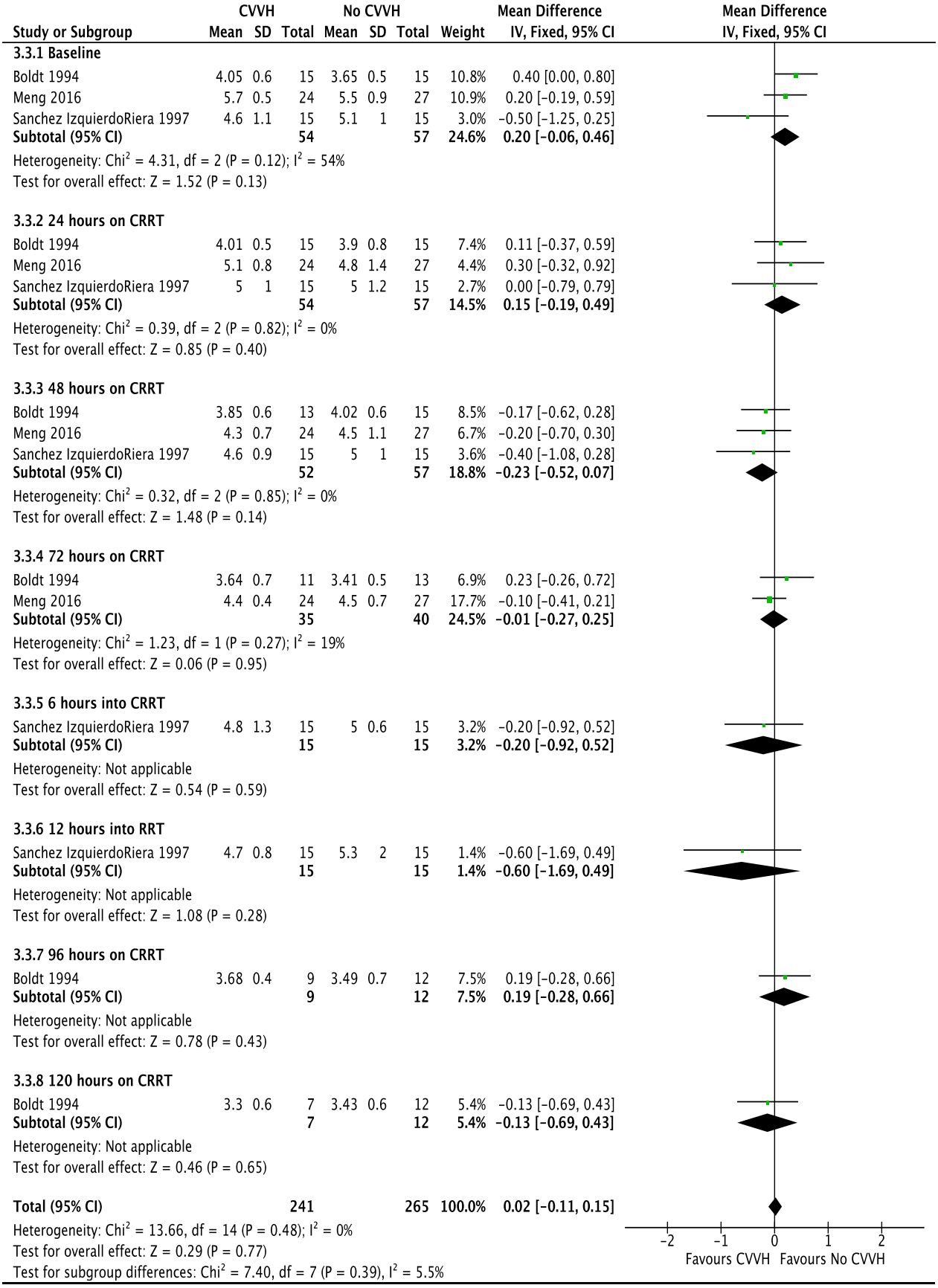
Study, Year of Pub.	Other bias (High/Low/ Unclear)	Intervention independent of other changes (High, Low, Unclear)	Shape of intervention effect prespecified (High, Low, Unclear)	Intervention unlikely to affect data collection (High, Low, Unclear)	Knowledge of interventions prevented during the study	Selective reporting (High, Low, Unclear)	Incomplete outcome data (High, Low, Unclear)
Heering., 1999	Low	High	Low	Low	Low	Low	High
Ganter., 2012	High	High	Low	Low	Low	Low	High
Forster., 2013	High	High	Low	Low	Low	Low	Low
Fiaccadori., 2002	Unclear	Low	Low	Low	Low	Low	Unclear
Eastwood., 2012	Unclear	Unclear	Low	Low	Low	Low	Unclear
Dai., 2016	Unclear	Unclear	High	Low	Low	Low	Low
Siebeck., 2018	High	Unclear	Low	Low	Low	Low	Low
Shin., 2011	Unclear	Unclear	Unclear	Low	Low	Unclear	Unclear
Mauritz., 1986	Unclear	Unclear	Low	Low	Unclear	Low	Unclear
Macias., 1991	High	Unclear	Unclear	Low	Unclear	Unclear	Low
Lafuente., 2016	High	Unclear	Unclear	Low	Low	Unclear	Unclear
Honoré., 2000	High	Unclear	Low	Unclear	Low	Low	Unclear
Hoffmann., 1996	High	High	Low	Unclear	Low	Low	Low
Cader Rizna., 2014	High	High	Unclear	Low	Low	Low	Unclear

Study, Year of Pub.	Other bias (High/Low/ Unclear)	Intervention independent of other changes (High, Low, Unclear)	Shape of intervention effect prespecified (High, Low, Unclear)	Intervention unlikely to affect data collection (High, Low, Unclear)	Knowledge of interventions prevented during the study	Selective reporting (High, Low, Unclear)	Incomplete outcome data (High, Low, Unclear)
Boldt., 1994	High	Unclear	Unclear	Low	Low	Low	Low
Biancofiore., 2003	Unclear	Unclear	Low	Low	Low	Low	Low
Bellomo., 1994[1]	High	High	Low	Low	Low	Low	Unclear
Bellomo., 1994[2]	Unclear	High	High	Low	Unclear	Low	Unclear
Bellomo., 1994[3]	Unclear	Unclear	Low	Low	Low	Low	Unclear
Bellomo., 2013	High	Low	Low	Low	Low	Low	Low
Bellomo., 1995[1]	Unclear	High	High	Low	Low	Low	Unclear
Bellomo., 1995[2]	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Abdo., 2012	High	Unclear	Low	Low	Low	Low	Low
Abd Elaziz., 2015	High	Unclear	Low	Low	Low	Low	Unclear

2.4.4 Effect of CVVH vs no CVVH on cardiac index

3 studies (total n = 506) assessed the effect of CVVH versus no CVVH on cardiac index (Figure 2.2). There was no significant mean difference in cardiac index at 24, 48 and 72 hours between patients treated with CVVH and those who did not receive CVVH (total mean difference 0.02 L/min/m^2; 95% CI -0.11 to 0.15; p = 0.77; I^2 = 0%).

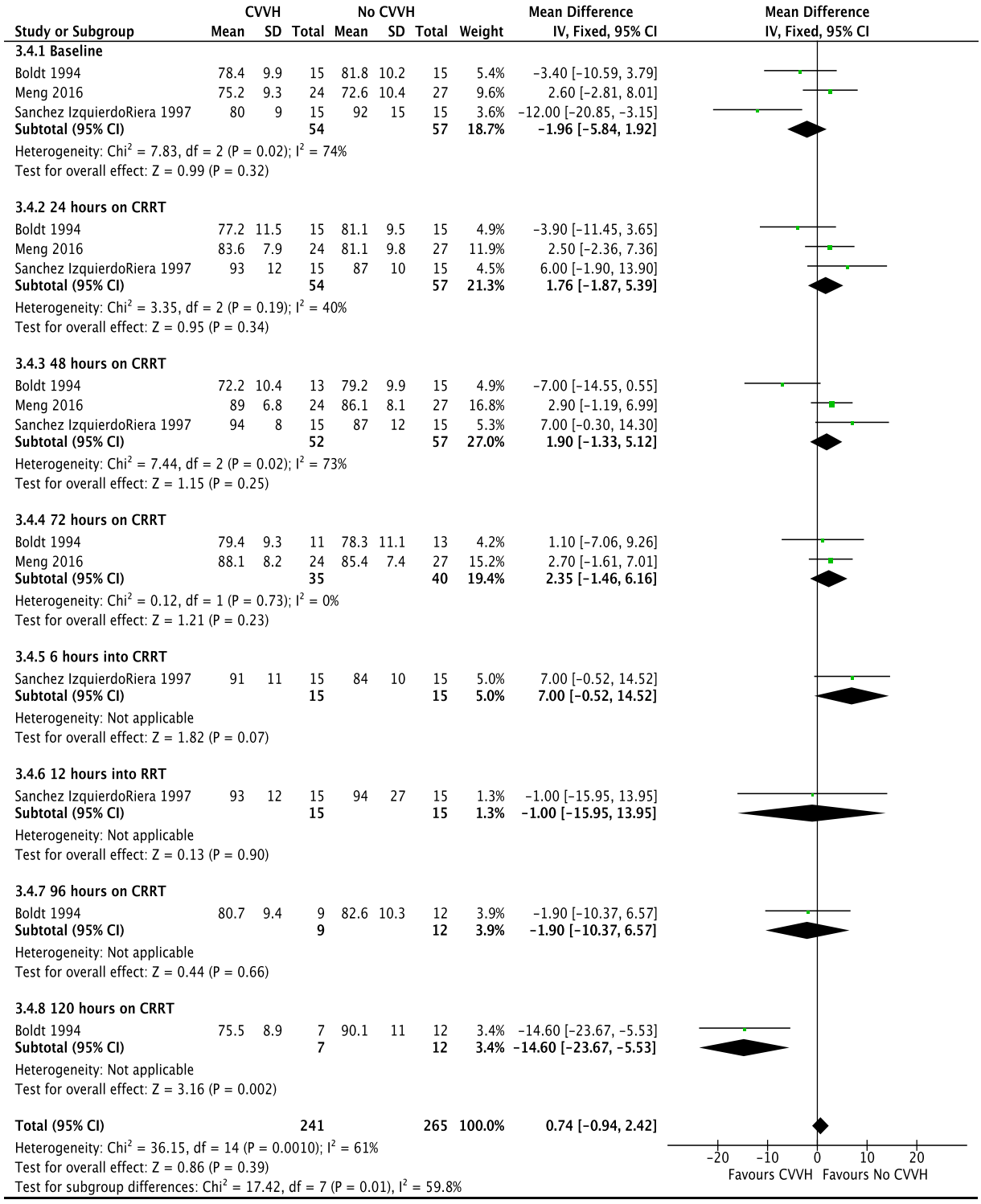
Figure 2.2: Forest plot for the effect of CVVH vs no CVVH on cardiac index



2.4.5 Effect of CVVH vs no CVVH on mean arterial pressure

Boldt., 1994 (n = 21) demonstrated a significant reduction in mean arterial pressure at 120 hours for patients on CVVH vs patients that were not treated with CVVH (mean difference -14.6 mm Hg; 95% CI -23.7 to -5.5; p = 0.002; Figure 2.3). However, there was overall no significant difference in mean arterial pressure for the 3 studies (total n = 506) that assessed this in patients treated with CVVH vs no CVVH; though with moderate heterogeneity present (total mean difference 0.74 mm Hg; 95% CI -0.94 to 2.42; p = 0.39; I^2 = 59.8%).

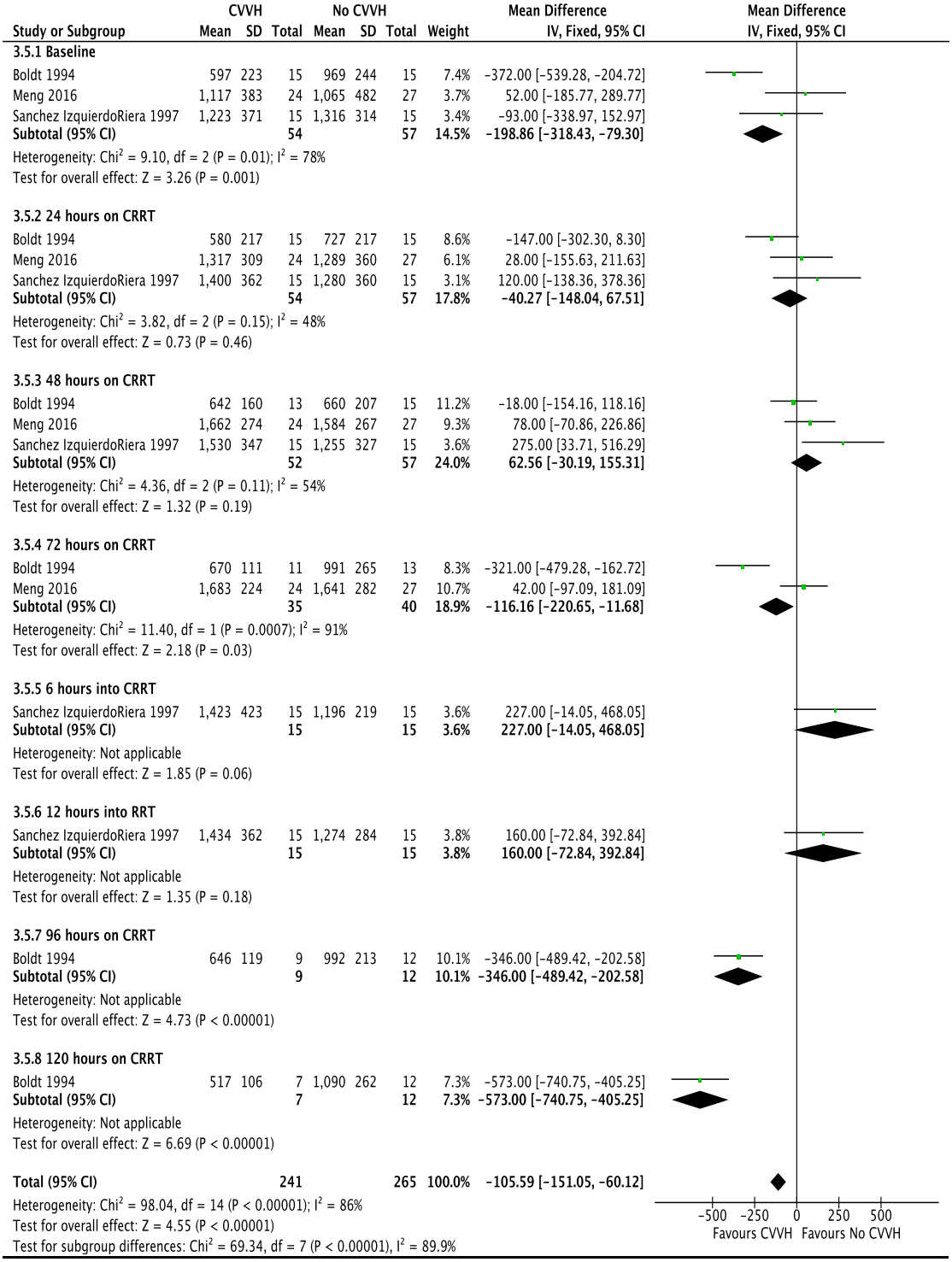
Figure 2.3: Forest plot of the effect of CVVH vs no CVVH on mean arterial pressure



2.4.6 Effect of CVVH vs no CVVH on systemic vascular resistance

3 studies (total n = 506) assessed the effect of CVVH versus no CVVH on systemic vascular resistance (Figure 2.4). Systemic vascular resistance was significantly lower for patients treated with CVVH compared to those who did not receive CVVH; both at baseline (mean difference -198.9 dyn.s.cm^{-5}; 95% CI -318.4 to -79.3; p = 0.001; I^2 = 78%) and at 72 hours into treatment (mean difference -116.2 dyn.s.cm^{-5}; 95% CI -220.7 to -11.7; p = 0.03; I^2 = 91%). Overall systemic vascular resistance was significantly lower for patients treated with CVVH compared to those who did not receive CVVH during the study period (total mean difference -105.6 dyn.s.cm^{-5}; 95% CI -151.1 to -60.1; p < 0.00001; I^2 = 86%). However, there was significant statistical heterogeneity present.

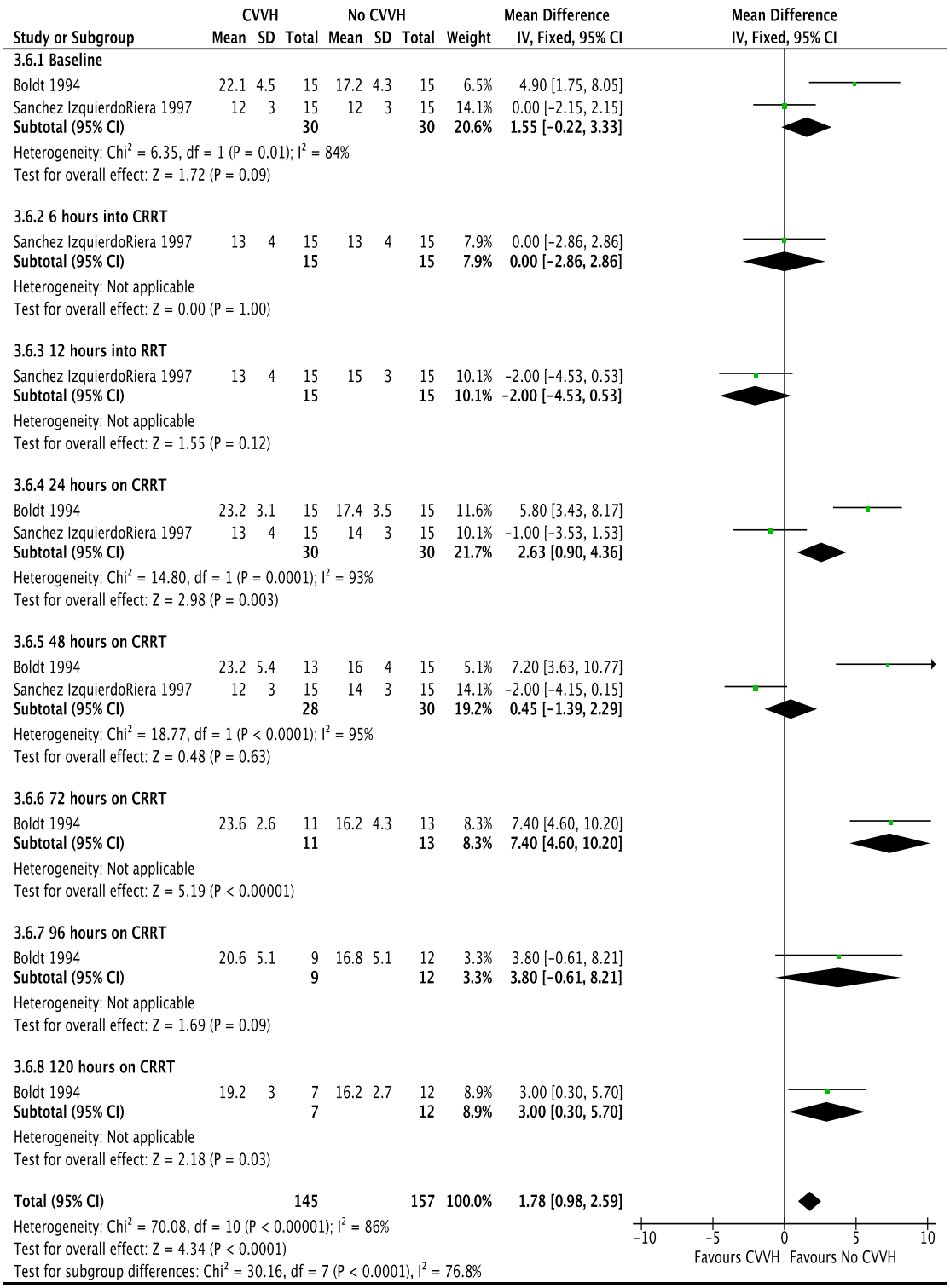
Figure 2.4: Forest plot of the effect of CVVH vs no CVVH on systemic vascular resistance



2.4.7 Effect of CVVH vs no CVVH on pulmonary capillary wedge pressure

2 studies (total n = 302) assessed the effect of CVVH versus no CVVH on pulmonary capillary wedge pressure (Figure 2.5). Pulmonary capillary wedge pressure was significantly higher at 24 hours in the group who were not treated with CVVH compared to those who were treated with CVVH (mean difference 2.6 mm Hg; 95% 0.9 to 4.4; $p = 0.003$; $I^2 = 93\%$). Overall pulmonary capillary wedge pressure was significantly higher throughout the study period for patients who were not treated with CVVH compared to those who were treated with CVVH (total mean difference 1.8 mm Hg; 95% CI 0.98 to 2.6; $p < 0.0001$; $I^2 = 77\%$). However, there was significant statistical heterogeneity present.

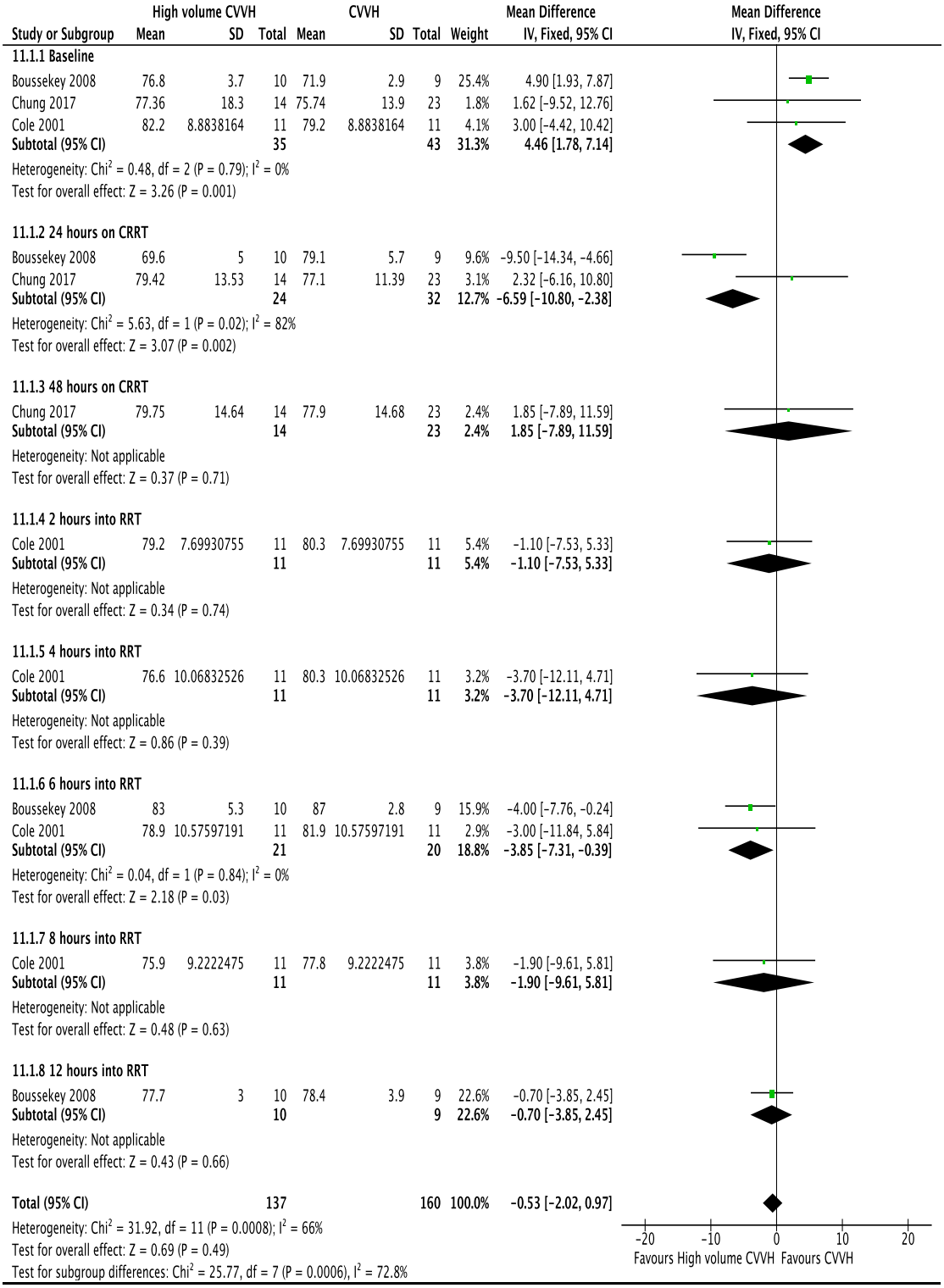
Figure 2.5: Forest plot of the effect of CVVH vs no CVVH on pulmonary capillary wedge pressure



2.4.8 Effect of high volume CVVH vs CVVH on mean arterial pressure

3 studies (total n = 297) assessed the effect of high volume CVVH versus CVVH on mean arterial pressure (Figure 2.6). At baseline, mean arterial pressure was significantly higher for patients treated with CVVH compared to those who were treated with high volume CVVH (mean difference 4.5 mm Hg; 95% CI 1.8 to 7.1 mm Hg; p = 0.001; I^2 = 0%). However, at 6 hours mean arterial pressure was significantly lower for patients treated with high volume CVVH compared to those who were treated with CVVH (mean difference -3.9 mm Hg; 95% CI -7.3 to -0.4; p = 0.03; I^2 = 0%). Mean arterial pressure was also significantly lower at 24 hours for patients treated with high volume CVVH compared to those who were treated with CVVH (mean difference -6.6 mm Hg; 95% CI -10.8 to -2.4; p = 0.002; I^2 = 82%). Overall, however, there was no significant difference in mean arterial pressure between those treated with high volume CVVH and CVVH at standard volume (total mean difference -0.5 mm Hg; 95% CI -2 to 0.97; p = 0.49; I^2 = 66%. There was moderate heterogeneity present.

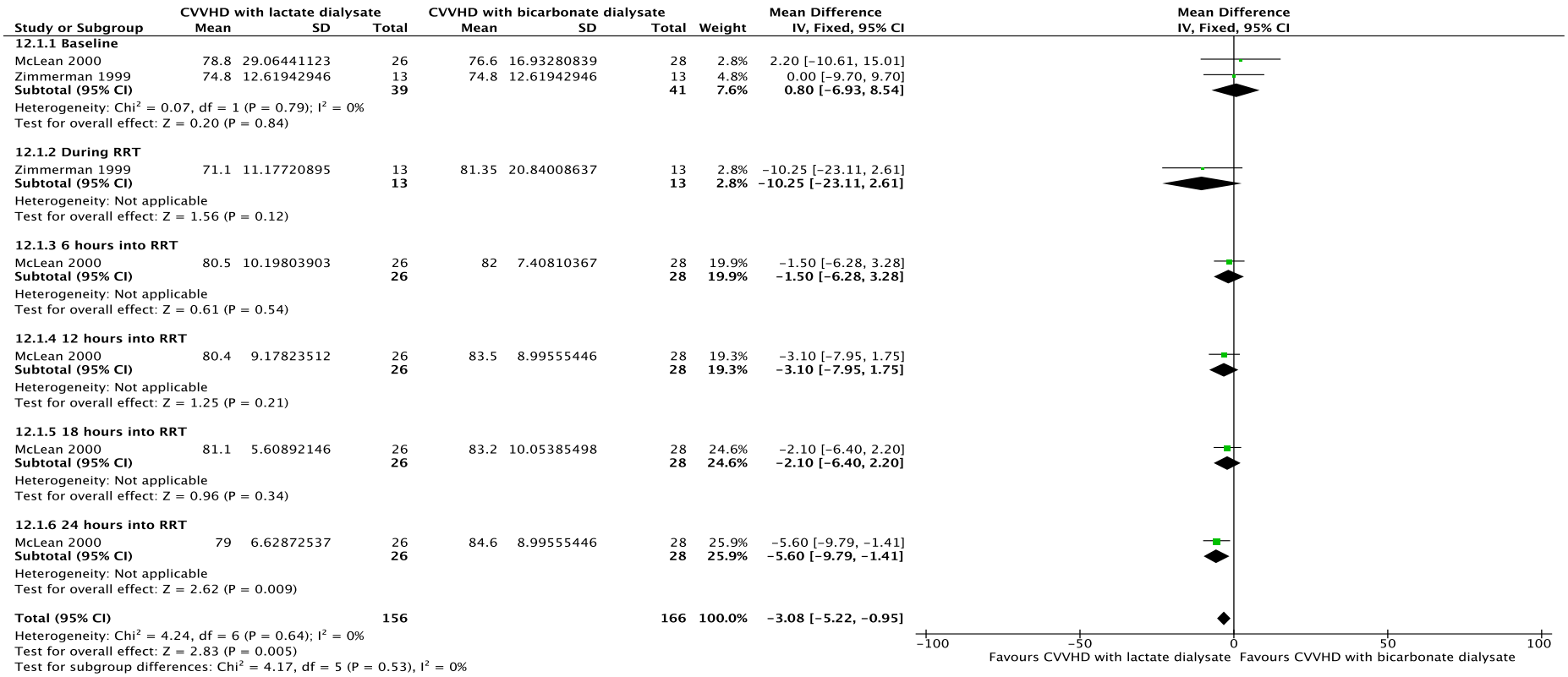
Figure 2.6: Forest plot for the effect of high volume CVVH vs CVVH on mean arterial pressure



2.4.9 Effect of CVVHD with lactate-buffered dialysate vs CVVHD with bicarbonate-buffered dialysate on mean arterial pressure

2 studies (total n = 322) assessed the effect of CVVHD with lactate-buffered dialysate vs CVVHD with bicarbonate-buffered dialysate on mean arterial pressure (Figure 2.7). McLean., 2000 (n = 54) found that mean arterial pressure was significantly lower at 24 hours into treatment for patients treated with CVVHD using lactate-buffered dialysate compared to patients treated with CVVHD using bicarbonate-buffered dialysate (mean difference -5.6 mm Hg; 95% -9.8 to -1.4; p = 0.009). When we pooled the results of the 2 studies, mean arterial pressure was overall significantly lower throughout the treatment period for patients treated with CVVHD using lactate-buffered dialysate compared to those treated with CVVHD using bicarbonate-buffered dialysate (total mean difference -3.1 mm Hg; 95% CI -5.2 to -0.95; p = 0.005; I^2 = 0%).

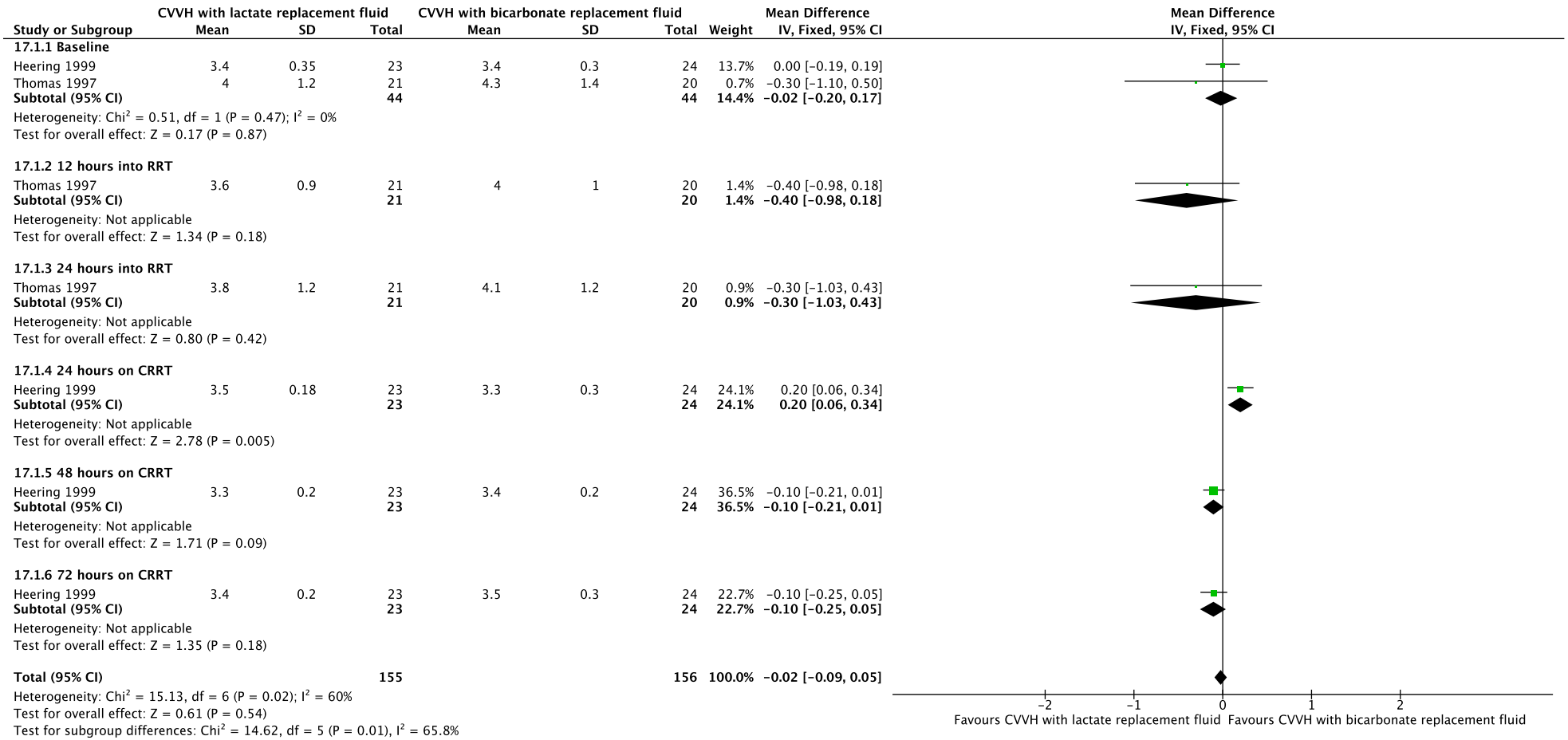
Figure 2.7: Forest plot of the effect of CVVHD with lactate vs CVVHD with bicarbonate dialysate on mean arterial pressure



2.4.10 Effect of CVVH with lactate replacement fluid vs CVVH with bicarbonate replacement fluid on cardiac index

2 studies (total n = 311) assessed the effect of CVVH with lactate replacement fluid vs CVVH with bicarbonate replacement fluid on cardiac index (Figure 2.8). Heering., 1999 found that cardiac index was significantly higher at 24 hours for patients treated with CVVH with bicarbonate replacement fluid compared to those treated with CVVH with lactate replacement fluid (mean difference 0.2 L/min/m^2; 95% CI 0.06 to 0.34; p = 0.005). However, there was no overall significant difference in cardiac index between patients treated with CVVH with lactate replacement fluid compared to those treated with CVVH with bicarbonate replacement fluid throughout the treatment period (total mean difference -0.02 L/min/m^2; 95% -0.09 to 0.05; p = 0.54; I^2 = 60%). There was moderate heterogeneity present.

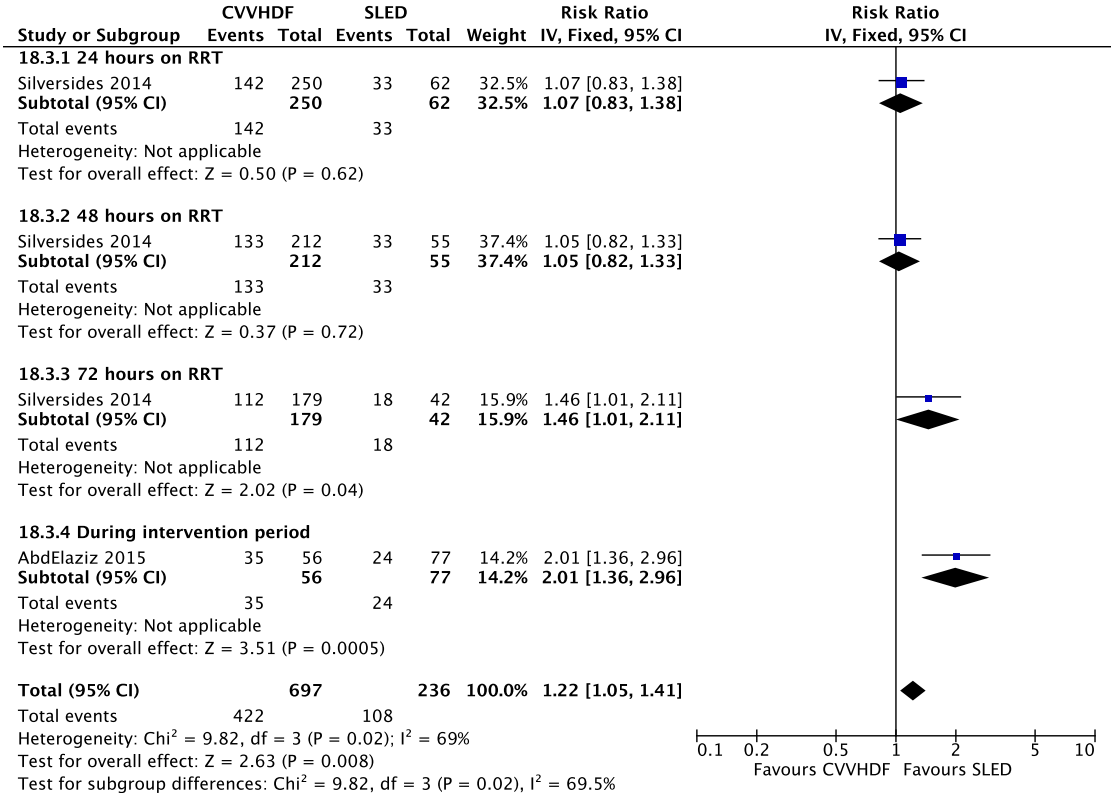
Figure 2.8: Forest plot of the effect of CVVH with lactate replacement fluid vs CVVH with bicarbonate replacement fluid on cardiac index



2.4.11 Effect of CVVHDF vs SLED on intradialytic hypotension

2 studies (total n = 933) assessed the effect of CVVHDF vs SLED on intradialytic hypotension (Figure 2.9). There was an overall significantly higher risk of intra-dialytic hypotension for patients on CVVHDF compared to those who received SLED during the study period (total risk ratio 1.22; 95% CI 1.05-1.41; p = 0.008; I^2 = 69%) but with significant heterogeneity present.

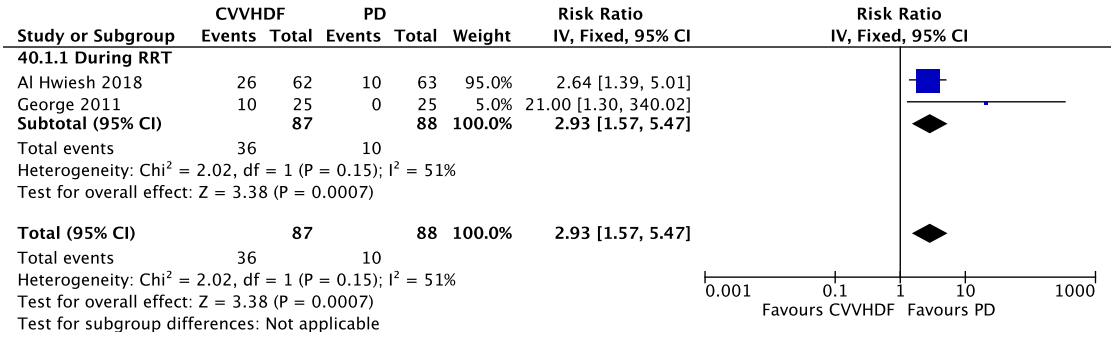
Figure 2.9: Forest plot of the effect of CVVHDF vs SLED on intradialytic hypotension



2.4.12 Effect of CVVHDF vs PD on hypotension

2 studies (total n = 175) assessed the effect of CVVHDF vs PD on hypotension (Figure 2.10). There was an overall significantly higher risk of hypotension for patients on CVVHDF compared to those who received PD during the study period (total risk ratio 2.93; 95% CI 1.57-5.47; p = 0.0007; I^2 = 51%) but with moderate heterogeneity present.

Figure 2.10: Forest plot of the effect of CVVHDF vs PD on hypotension



2.5 Discussion

This systematic review and meta-analysis of 92 randomised controlled trials and prospective cohort studies assessed the effect of CRRT on hemodynamic outcomes in comparison with either other dialytic modalities or with CRRT at different prescriptions/in different patient populations. We were only able to include a maximum of 3 studies in our meta-analyses as a huge number of varying hemodynamic parameters were used as outcome measures in different studies; making pooled effect estimates difficult. We found that there was no significant difference in cardiac index or mean arterial pressure between patients treated with CVVH compared to those who were not treated with CVVH, though systemic vascular resistance was significantly lower for patients treated with CVVH. Pulmonary capillary wedge pressure was also significantly higher for patients who were not treated with CVVH compared to those who were treated with CVVH throughout the study period. There was no significant difference in mean arterial pressure between patients treated with high volume CVVH compared to conventional volume CVVH. Mean arterial pressure was

significantly lower for patients treated with CVVHD with lactate-buffered dialysate compared to those treated with CVVHD with bicarbonate-buffered dialysate. However, there was no significant difference in cardiac index between patients treated with CVVH with lactate-buffered replacement fluid compared to those treated with CVVH with bicarbonate-buffered replacement fluid. The risk of intradialytic hypotension was significantly higher for patients treated with CVVHDF compared to those treated with SLED. Similarly, the risk of hypotension was significantly higher for patients treated with CVVHDF compared to PD. There was significant heterogeneity present for all outcomes apart from the finding of reduced mean arterial pressure with CVVHD using lactate-buffered dialysate compared to bicarbonate-buffered dialysate. However, given the small number of studies that could be included in each meta-analysis to produce a pooled effect estimate, we did not have sufficient power to perform subgroup analyses or meta regression to assess whether differences in baseline characteristics could account for the large amounts of heterogeneity observed. Many of the studies, particularly those performed with IHD, had a small number of participants which additionally affected our ability to produce accurate pooled effect estimates and which likely contributed to the significant heterogeneity observed with most of the results. The variable terminology utilised for haemodynamic outcomes in the literature also made it difficult to pool studies together in a reliable manner to perform a meta-analysis.

To our knowledge, this is the first systematic review to address the question of whether CRRT affects haemodynamic outcomes in comparison with either other dialytic modalities or with CRRT at different prescriptions/in different patient populations. A pre-print systematic review by Russo., 2019 compared haemodynamic outcomes between CRRT and other dialytic modalities but only included data from randomised controlled trials so was unable to perform a meta-analysis. Their systematic review noted qualitatively that CVVH was associated with a reduction in heart rate after 1 and 4 hours, as well as an increase in systolic blood pressure after 0.5 and 2 hours, in comparison with IHD, but these results were based on the findings of just one RCT (Jones., 2001) and were not reproduced in other studies. By including prospective cohort studies as part of our search strategy for our systematic review and meta-analysis, we were thereby able to increase the statistical power and generalisability of our results. This also allowed us to include studies which compared CRRT at different

prescriptions or between different populations; which added granularity to our results and provided an in-depth investigation of the effect of changes to CRRT dose, modality, anti-coagulation, blood flow rate and membrane type on hemodynamic outcomes. Despite these strengths, inferences from our study are limited due to significant statistical heterogeneity and due to reduced ability to produce well-powered pooled effect estimates as a result of wide variability in the haemodynamic parameters (both directly measured and calculated) that were used as primary and secondary outcomes in these studies.

Other systematic reviews of CRRT have focused on whether CRRT is advantageous over other dialytic modalities. Nash., 2017 found that there was no advantage associated with use of any particular RRT modality with regard to mortality, RRT dependence or length of stay. Brain., 2017 found a 44% lower rate of filter failure with CVVHDF compared to CVVH in a meta-analysis of non-anticoagulant factors associated with filter life in CRRT. Indeed, Rewa., 2017 found that filter life was one of the most important quality indicators for CRRT care in their systematic review which also identified small solute clearance, bleeding, delivered dose and treatment interruption as other key quality indicators for CRRT management. Notably, other potential side-effects of CRRT, such as hemodynamic instability, electrolyte derangements and inadvertent removal of important medications such as antibiotics, were not identified as important quality indicators for CRRT management; largely because these were not frequently assessed as outcomes of interest in these studies.

Our systematic review therefore adds important information to the risk and incidence of haemodynamic instability as an adverse event associated with CRRT. A surprisingly small number of clinical trials in the CRRT literature have included haemodynamic adverse events as secondary outcomes; which has limited the ability of previous investigators to produce pooled estimates of the risk of the adverse events on CRRT. A recent Cochrane systematic review of intensity of RRT included only a maximum of 3 randomized controlled trials in its pooled estimates of adverse events on CRRT (Fayad., 2016). Our results are largely in keeping with those found in the Cochrane review and elsewhere in the literature which note that increased exposure to CRRT – either through intensity of dosing or early initiation on treatment - is associated with increased risk of arrhythmias, hypotension and electrolyte losses (the STARRT-AKI Investigators., 2020). These findings emphasise the need for careful

CRRT prescribing with the aid of evidence-based guidelines that support weight-based dosing and that reserve intensive CRRT dosing for specific circumstances, e.g. post cardiac surgery where careful control of acidaemia may be needed in the setting of right ventricular failure, in order to minimise the risk of haemodynamic and other adverse events associated with higher intensity CRRT (Vidal., 2009). The increased risk of hypotension on CVVHDF in contrast to SLED or PD lends further credence to the potential utility of these dialytic modalities in the critical care setting for patients with AKI-RRT; where resources and education are available to support their wider use. Our finding regarding the significantly lower mean arterial pressure associated with use of lactate-based dialysate for CVVHD in comparison with bicarbonate-based dialysate is also of interest, though use of lactate-buffered dialysate has largely been superseded by bicarbonate-buffered solutions in the present day, so this may not have as much relevance to present day practices as our other findings.

2.6 Conclusions

In summary, our systematic review and meta-analysis assessing the effect of CRRT on haemodynamic outcomes in comparison with either other dialytic modalities or with CRRT at different prescriptions showed increased risk of hypotension with CVVHDF compared to PD and SLED; reduced mean arterial pressure during treatment with CVVHD using lactate-buffered dialysate compared to bicarbonate-buffered dialysate and reduced systemic vascular resistance with use of CVVH compared to no CVVH but no other significant risk of adverse haemodynamic outcomes associated with CRRT at any other prescription. Our conclusions are limited by the relatively small number of studies that could be pooled for meta-analysis due to wide variety of hemodynamic measures utilised in individual studies. Large dedicated randomised controlled trials with haemodynamic and other adverse events as primary endpoints of CRRT treatment will be needed to determine the true incidence of haemodynamic adverse events according to CRRT prescription.

CHAPTER 3

Predictors of CRRT-associated hypotension in the ICU

3.1 Abstract

Introduction: Continuous renal replacement therapy (CRRT) remains the mainstay of supportive therapy for severe acute kidney injury (AKI) in the intensive care unit (ICU), but there may be treatment-associated adverse events due to excess removal of small solutes. We investigated the effect of potentially modifiable CRRT-related treatment factors on the risk of severe hypotension.

Methods: Using data recorded during the Acute Renal Failure Trial Network (ATN) trial, we assessed the incidence of severe hypotension (defined as a vasopressor-inotropic score > 18) in those randomised to higher (35 ml/kg/hour) versus lower intensity (20 ml/kg/hour) CRRT treatment. We then modelled the effect of CRRT-related treatment factors on the risk of severe hypotension on CRRT, including treatment dose, ultrafiltration rate, blood flow rate, ionised calcium level and type of anti-coagulation used.

Results: Of 1124 individuals enrolled in the ATN Trial, 786 were managed with CRRT (381 in standard intensity versus 405 higher intensity cohort). The median vasopressor-inotropic score (VIS) was 5 (interquartile range 0-18). 470/786 (59.8%) patients experienced severe hypotension during the trial, defined by a VIS score ≥ 18. A serum ionised calcium < 1.02 mmol/L was associated with a higher risk of severe hypotension compared to a serum calcium > 1.02 mmol/L (hazard ratio 2.0; 95% CI 1.5-2.6). There was no significant difference in the risk of hypotension associated with other CRRT treatment factors.

Conclusions: Of the CRRT treatment factors studied, hypocalcaemia with a serum ionised calcium < 1.02 mmol/L was associated with a significantly increased risk of treatment-associated hypotension. Further studies will be required to assess whether strict treatment targets for management of hypocalcaemia on CRRT will help to improve the risk of CRRT-associated hypotension in the future.

3.2 Introduction

Continuous renal replacement therapy (CRRT) is frequently used to treat patients with acute kidney injury (AKI) in the critical care setting (Koyner., 2014; Lombardi., 2014). CRRT was initially introduced for the treatment of haemodynamically unstable patients with AKI for whom conventional intermittent dialytic modalities can exacerbate hypotension. Nevertheless, hypotension on CRRT is common. Large retrospective cohort ICU studies have shown that up to 43% of patients experience new onset hypotension in the first hour after CRRT initiation (Akhoundi., 2015; Uchino., 2007).

Hypotension on CRRT is associated with a higher risk of early mortality and can also lead to early withdrawal of therapy due to treatment intolerance (Silversides., 2014; Shawwa., 2019; Tatum., 2017., Katayama., 2016). It is unclear whether modifiable CRRT treatment factors contribute to an increased risk of hypotension for this vulnerable patient population. Hypocalcaemia is common in the setting of critical illness and can be exacerbated by electrolyte losses during CRRT (Morimatsu., 2002). It may increase the risk of CRRT-associated hypotension due to its known effects on systemic vasodilation and reversible depression of left ventricular function (Jentzer., 2018; Newman., 2014). Similarly, faster rates of ultrafiltration may also give rise to increased risk of treatment-associated hypotension due to volume depletion and haemodynamic stress causing increased rates of arrhythmia and myocardial stunning (Silversides., 2014; Burton., 2009).

To test whether hypotension on CRRT is affected by CRRT treatment factors, we performed a secondary analysis of the ATN trial, a randomised controlled trial of intensive vs. less-intensive RRT (VA/NIH Acute Renal Failure Trial Network., 2008). Eligible patients were randomized to receive intensive RRT (intermittent haemodialysis (IHD) six times a week or CRRT at a dose of 35 ml/kg/hour) or less intensive RRT (IHD three times a week or CRRT at a dose of 20 ml/kg/hour). The use of IHD or CRRT was based on haemodynamic stability. We wished to assess whether modifiable CRRT treatment factors are associated with a higher risk of hypotension on CRRT treatment days.

3.3 Methods

3.3.1 Study design and population

The ATN trial was a multi-centre randomised controlled trial performed at 27 VA and university-affiliated health centres between November 2003 and July 2007 (VA/NIH Acute Renal Failure Trial Network., 2008). Eligible patients were 18 years or older, critically ill with acute kidney injury (AKI) requiring renal replacement therapy and accompanied by sepsis or failure of at least one non-renal organ system. Patients were randomly assigned to two different intensities of renal replacement therapy. In the group receiving the intensive-therapy strategy, intermittent haemodialysis and sustained low-efficiency dialysis (SLED) were provided six times per week and continuous venovenous hemodiafiltration was prescribed to provide a total effluent flow rate of 35 ml per kilogram of body weight per hour. In the less-intensive strategy, intermittent haemodialysis and sustained low-efficiency dialysis were provided three times per week and continuous veno-venous haemodiafiltration was prescribed to provide a total effluent flow rate of 20 ml per kilogram per hour. Assigned interventions were delivered for up to 28 days after randomisation or until renal recovery, discharge from the ICU, withdrawal of care, or death. Patients were followed for up to 60 days to ascertain the primary end point of all-cause mortality. Patients were excluded if they had >24 hrs CRRT or 1 session of haemodialysis (HD) prior to randomisation, expected survival <28 days secondary to an underlying chronic condition or baseline renal disease (serum creatinine >2mg/dL (177 μmol/L) in males and >1.5 mg/dL (133 μmol/L) in females).

Of 1124 individuals enrolled in the ATN Trial, 786 were managed with CRRT for at least one day (N = 381 randomised to higher intensity and 405 randomised to lower intensity therapy).

3.3.2 Exposures and Outcomes

We obtained de-identified data from the National Institute of Diabetic and Digestive and Kidney Diseases ATN study data repository. The study protocol was approved by the Partners Institutional Review Board. Demographic data (age, gender, race), co-morbid data (high blood pressure, diabetes, malignancy, Sequential Organ Failure Assessment (SOFA) score, congestive Heart Failure, previous myocardial infarction, chronic hypoxaemia) along

with weight were recorded at baseline for all study participants. The primary exposure of interest was CRRT treatment-related factors including the randomised treatment assignment of intensive vs less intensive RRT, CRRT ultrafiltration rate, type of anti-coagulation used, daily serum ionised calcium measurement on CRRT where available and CRRT blood flow rate.

The primary outcome measure was severe hypotension during CRRT. Severe hypotension was defined as a vasopressor-inotropic score (VIS) ≥ 18 (> 75th percentile for VIS scores in this cohort), recorded at any time from day 0-28 of the study period. The vasopressor-inotropic score (VIS) was introduced in paediatric critical care literature by Wernovsky et al (1995) in order to standardize the total hourly rate of vasopressor and inotropic agents administered by applying an equivalent value for each according to relative potency (Wernovsky., 1995; Gaies., 2010). Since then, the VIS score has been validated in studies of adult critically ill patients, with scores > 20 generally taken to indicate severe hypotension as they are associated with mortality, length of ICU stay and need for mechanical ventilation and renal replacement therapy among other indicators of morbidity in the intensive care setting (Nguyen., 2013; Kara., 2019). We restricted all analyses to study days in which CRRT rather than IHD/SLED was performed. Where patients received alternating CRRT and IHD/SLED courses, we restricted all analyses to the first course of CRRT that patients received.

3.3.3 Statistical analysis

Continuous variables were examined graphically and recorded as means (+/- SDs) for normally distributed data or medians (with IQRs) for non-normally distributed data. Comparisons were made using T tests or Wilcoxon rank sum tests as appropriate. Categorical variables were examined by frequency distribution and recorded as proportions. Repeated measures were assessed using generalised linear models with a repeated effect for individual patients. The primary outcome was the risk of severe hypotension, defined as a vasopressor-inotropic score (VIS) ≥ 18 on CRRT-treatment days over the study according to individual CRRT treatment factors (CRRT treatment dose, ultrafiltration rate, anticoagulation used, ionised calcium and CRRT blood flow rate).

The primary analysis was a Cox proportional sub-distribution hazards (competing risk) regression model which compared the risk of severe hypotension over the 0-28 day study period according to individual CRRT treatment factors by using a model that accounted for correlated repeated observations within subjects while also censoring for the competing risk of death. Ultrafiltration rate and CRRT blood flow rates were divided into quartiles to aid interpretation of results. Anti-coagulation was divided into citrate and non-citrate based anti-coagulation. Ionised calcium was divided into two categories according to values < or ≥ 1.02 mmol/L.

We fitted a series of multivariable models. We started with a univariate analysis that assessed the effect of the CRRT treatment factor on the risk of hypotension. Multivariate Model 1 added hospital and ICU length of stay, study site and baseline VIS score to the CRRT treatment factor. Multivariate Model 2 added illness severity scores and markers of organ failure; including mechanical ventilation, APACHE II (Acute Physiology and Chronic Health Evaluation) score, baseline total SOFA (Sequential Organ Failure Assessment) score, Cleveland Clinic Acute Renal Failure score, oliguria, age, sepsis, chronic hypoxaemia and pulmonary artery systolic pressure to the existing model. All models were implemented in SAS (SAS Institute Inc., Cary, NC) using PROC PHREG. A two-tailed p value < 0.05 was considered evidence of statistical significance for all outcomes.

3.4 Results

3.4.1 Baseline characteristics of patients who did/did not experience severe hypotension

Of 1124 individuals enrolled in the ATN Trial, 786 were managed with CRRT. 470/786 (59.8%) patients experienced severe hypotension on 1452/5613 (25.9%) CRRT treatment days during the study period, with severe hypotension occurring most frequently on days 1 and 2 of treatment (Figure 3.1). These patients had a shorter hospital (9.4 vs 11.9 days; p = 0.03) and ICU length of stay (5.8 vs 7.5 days; p = 0.004) prior to randomisation than those who did not experience severe hypotension during the trial (Table 3.1). Patients with severe hypotension were more likely to be mechanically ventilated (90.9% vs 83.9%; p =

0.004). They also had higher APACHE II (28.6 vs 25.2; p < 0.0001), total SOFA (16.3 vs 13.7; p < 0.0001) and Cleveland Clinic ICU Acute Renal Failure scores (13.1 vs 11.8; p < 0.0001) and were more likely to be oliguric (83.8% vs 80%; p = 0.04) at the time of randomisation.

Figure 3.1: Temporal distribution of mean vasopressor-inotropic score (VIS) on continuous renal replacement therapy (CRRT) treatment days

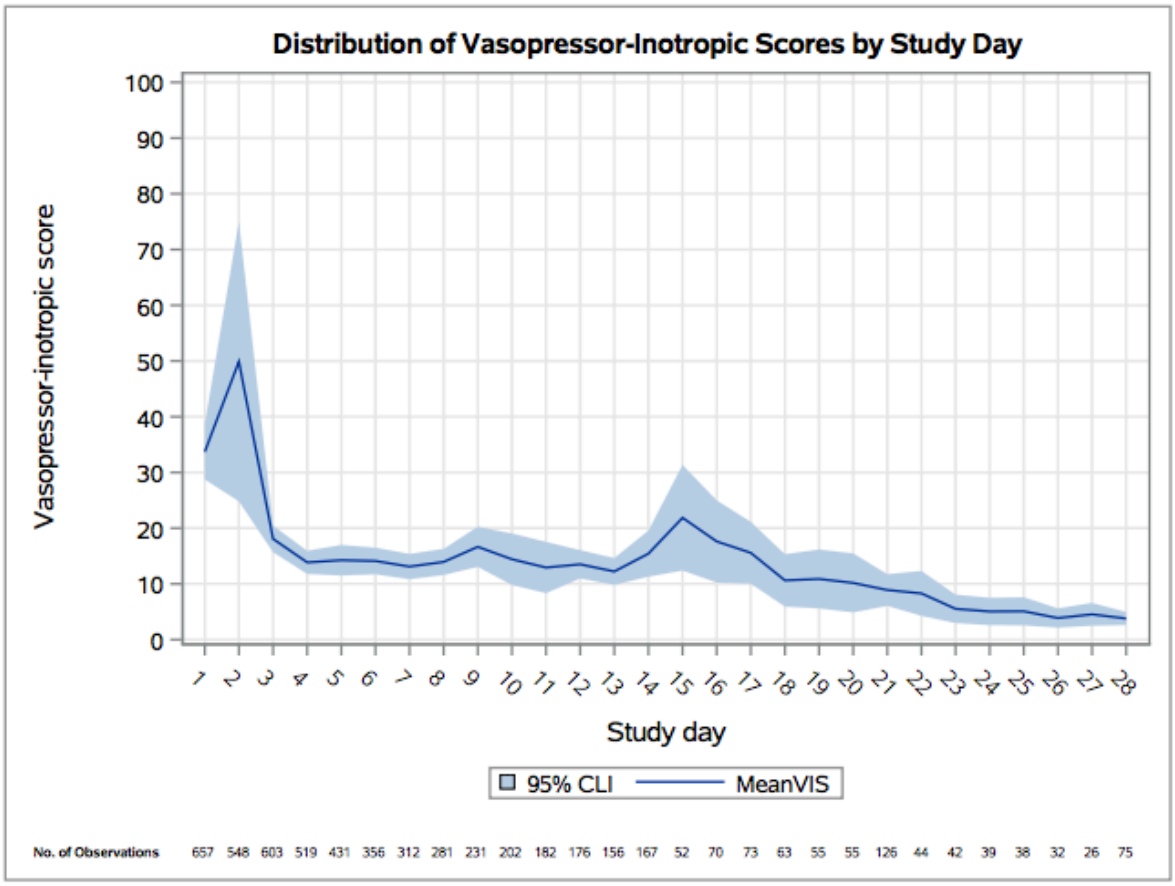


Table 3.1: Baseline characteristics of the CRRT patients who subsequently developed severe hypotension*

Characteristic	Not severe hypotension (n = 316)	Severe hypotension (n = 470)	P-value**
Age (years)	59.2 +/- 15.7	59.9 +/- 15.2	0.58
Gender (no./no. with data)			
Male	216/316 (68.4%)	323/470 (68.7%)	0.94
Female	100/316 (31.7%)	147/470 (31.3%)	
Race (no./no. with data)			
White	237/316 (75%)	356/470 (75.7%)	0.28
Black	42/316 (13.3%)	70/470 (14.9%)	
Hispanic	25/316 (7.9%)	31/470 (6.6%)	
Other	12/316 (3.8%)	13/470 (2.8%)	
Renal function before onset of acute kidney injury			
Serum creatinine – mg/dl	1.09 +/- 0.35	1.11 +/- 0.52	0.53
Cause of acute kidney injury (no./no. with data)			
Ischemia	249/304 (81.9%)	395/456 (86.6%)	0.08
Nephrotoxins	77/287 (26.8%)	105/433 (24.3%)	0.48
Sepsis	157/291 (54%)	264/446 (59.2%)	0.17
Multifactorial	171/294 (58.2%)	275/443 (62.1%)	0.32
Weight before acute illness - kg	84.8 (+/- 19)	82.5 (+/- 18.6)	0.09
Length of stay before randomization - days			
Hospital	11.9 +/- 17.8	9.4 +/- 11.1	0.03
ICU	7.5 +/- 9.6	5.8 +/- 5.7	0.004
Charlson comorbidity index	2.6 +/- 2.5	2.5 +/- 2.6	0.44
Age-adjusted Charlson comorbidity index	4.3 +/- 3	4.2 +/- 3	0.68
Mechanical ventilation (no./no. with data)	265/316 (83.9%)	427/470 (90.9%)	0.004
APACHE II score	25.2 +/- 7.1	28.6 +/- 6.7	< 0.0001
SOFA organ-system score			
Respiratory	2.3 +/- 1	2.5 +/- 1.1	0.003
Coagulation	1.4 +/- 1.2	1.5 +/- 1.2	0.2
Liver	1.5 +/- 1.3	1.7 +/- 1.3	0.01
Cardiovascular	1.9 +/- 1.5	3.4 +/- 1.2	< 0.0001
Central nervous system	2.4 +/- 1.4	3.0 +/- 1.2	< 0.0001
Total	13.7 +/- 3.2	16.3 +/- 2.9	< 0.0001
Cleveland Clinic ICU Acute Renal Failure Score	11.8 +/- 3.4	13.1 +/- 2.9	< 0.0001
BUN at initiation of RRT – mg/dl	65.6 +/- 34.5	62.1 +/- 32.1	0.22
Cardiovascular SOFA score - no. (%)			
0-2	176/316 (55.7%)	66/467 (14.1%)	< 0.0001
3-4	140/316 (44.3%)	401/467 (85.9%)	
Oliguria – no. (%)			
No	70/316 (22.2%)	76/470 (16.2%)	0.04
Yes	305/381 (80.0%)	394/470 (83.8%)	

*Plus-minus values are means +/- SD. Percentages are based on the number of patients without missing data. Possible scores range from 0 to 6 for each of the 17 indicators on the Charlson comorbidity index, 0 to 71 for the Acute Physiology and Chronic Health Evaluation (APACHE) II Score, and 0-4 for each of six organ systems for Sequential Organ Failure Assessment (SOFA) (with the renal-system score not reported separately but included in the calculation of the total SOFA score); higher scores indicate more severe organ dysfunction. The Cleveland Clinic Intensive Care Unit (ICU) Acute Renal Failure score can range from 1 to 20, with higher scores predictive of increased risk of death.

**P-values were calculated with the use of Fisher's exact test for categorical variables and the T-test for continuous variables.

3.4.2 Association between CRRT-related factors and vasopressor-inotropic score

Baseline VIS scores were significantly higher for patients who subsequently underwent CRRT with higher ultrafiltration rates than those with lower ultrafiltration rates (11.1 vs 20.5 vs 32.1 vs 46.9 according to ascending quartile of ultrafiltration rate; p = 0.01; Table 3.2). Baseline VIS scores were also significantly higher for patients with lower serum ionised calcium levels during the study period, than for those with higher serum ionised calcium levels during the study period (44.6 +/- 25.2; p = 0.002). Using a repeated measures analysis in a generalized linear model to compare changes in VIS score according to CRRT treatment factors over the study period, we found that the estimated difference in VIS during the study period was significantly higher for patients with ionised calcium < 1.02 mmol/L compared to those with ionised calcium ≥ 1.02 mmol/L (35 +/- 6.4; p = 0.04). There was no significant difference in estimated VIS according to CRRT treatment intensity, type of anti-coagulation used or quartiles of CRRT ultrafiltration or blood flow rates (Table 3.3).

Table 3.2: Baseline VIS scores according to CRRT treatment factor

CRRT treatment factor	Baseline VIS score	P-value
Treatment intensity		
Less intensive CRRT	33.6 +/- 79.6	0.98
Intensive CRRT	33.8 +/- 75	
Ultrafiltration rate		
< 25 ml/hour	11.1 +/- 11.1	0.01
25-100 ml/hour	20.5 +/- 29.8	
100-194 ml/hour	32.1 +/- 93.8	
> 194 ml/hour	46.9 +/- 83.1	
Anti-coagulation		
Citrate anti-coagulation	33.9 +/- 82.1	0.82
Non-citrate anti-coagulation	32.7 +/- 45.9	
Ionized calcium		
< 1.02 mmol/L	44.6 +/- 80.5	0.002
≥ 1.02 mmol/L	25.2 +/- 36.1	
CRRT blood flow rate		
< 120 ml/min	45.5 +/- 99.6	0.12
120-150 ml/min	41.1 +/- 128.8	
150-180 ml/min	25.7 +/- 34.6	
> 180 ml/min	32.3 +/- 50	

Table 3.3: Comparison of differences in vasopressor-inotropic score (VIS) +/- standard error during the study period according to CRRT treatment characteristics.

CRRT treatment factor	Estimated difference in VIS +/- standard error	P-value*
CRRT treatment dose (reference 20 ml/kg/hour)		
35 ml/kg/hour	2.6 +/- 3.2	0.41
Ultrafiltration rate (reference < 25 ml/hour)		
25-100 ml/hour	-0.3 +/- 9.8	0.98
100-194 ml/hour	4.3 +/- 9.6	0.66
> 194 ml/hour	11.7 +/- 9.7	0.23
Anti-coagulation (reference non-citrate anticoagulation)		
Citrate anti-coagulation	0.4 +/- 3.9	0.9
Ionized calcium (reference ≥ 1.02 mmol/L)		
< 1.02 mmol/L	35 +/- 6.4	< 0.0001
CRRT blood flow rate (reference < 120 ml/min)		
120-150 ml/min	-2.5 +/- 5.1	0.62
150-180 ml/min	-1.8 +/- 4.4	0.69
>180 ml/min	-3.1 +/- 4.6	0.5

*P values were calculated using generalized linear models with a repeated effect for individual patients.

3.4.3 Management of CRRT according to subsequent development of severe hypotension (unadjusted analyses)

There were a total of 13576 study days in the trial; which reduced to 5613 CRRT therapy days once other RRT treatment modalities were excluded and with restriction of our analysis to the first CRRT treatment course undergone by each patient. Out of 786 patients managed with CRRT, 389 (49.5%) received at least one day of HD/SLED during the course of the trial. CRRT therapy characteristics for patients who did and did not subsequently develop severe hypotension are summarised in Table 3.4. Patients who experienced severe hypotension underwent a faster hourly ultrafiltration rate on CRRT than those who did not experience severe hypotension (159.2 vs 129.3 ml/hour). Patients who experienced severe hypotension also more frequently received citrate anti-coagulation (24.5% vs 19.5%), while those who did not experience severe hypotension more frequently received heparin anti-coagulation (19.9% vs 14%).

Table 3.4: Management of CRRT according to subsequent development of severe hypotension*

Characteristic of therapy	Not severe hypotension (n = 316)	Severe hypotension (n = 470)
CRRT treatments provided – no.	3709	1247
Days of CRRT – no. per patient	13.1 +/- 7.6	11.3 +/- 7.1
Daily duration of therapy/patient - hours		
Median (interquartile range)	21 (15-24)	21 (14-24)
Blood flow – ml/min	145.9 +/- 37	146.8 +/- 37.7
Dialysate flow – ml/hr	1136.1 +/- 424.8	1124.5 +/- 440.2
Replacement flow – ml/hr	1127 +/- 406.6	1116.3 +/- 396.9
Net ultrafiltration – ml/hr	129.3 +/- 129.6	159.2 +/- 254.6
24 hour effluent volume - liters	42.5 +/- 21.2	42.7 +/- 20.3
Anticoagulant – no. of treatments (%)		
None	2124 (57.4)	717 (57.5)
Heparin	738 (19.9)	174 (14)
Citrate	723 (19.5)	305 (24.5)
Other	117 (3.2)	50 (4)

*Plus-minus values are means +/- SD. The therapy phase was defined as the time of randomisation through the time of discontinuation of study therapy. For continuous venovenous hemodiafiltration, each day of therapy was counted as a treatment.

3.4.4 Univariate and Multivariate analysis

We fitted a Cox proportional sub-distribution hazards model with a competing risk for death and an aggregate function to account for correlated repeated measures within subjects in order to assess the risk of hypotension according to CRRT treatment intensity, ultrafiltration rate, type of anti-coagulation, ionised calcium and CRRT blood flow rate respectively (Table 3.5; Figure 3.2). In a multivariate model adjusted for hospital and ICU length of stay pre randomization, study site, baseline VIS, mechanical ventilation, baseline APACHE II score, baseline total SOFA score, baseline Cleveland Clinic Acute Renal Failure score, oliguria, age, sepsis, chronic hypoxaemia and pulmonary artery systolic pressure, there was an increased risk of hypotension for patients with serum ionised calcium < 1.02 mmol/L compared to those with ionized calcium ≥ 1.02 mmol/L (hazard ratio 2.0; 95% CI 1.5-2.6; $p < 0.0001$); though measurement of this laboratory parameter was not mandated for all patients in the trial and was therefore missing in many cases. In a sensitivity analysis, we added arterial pH to the multivariate model to ensure that the risk of hypotension associated with hypocalcaemia was not caused by concomitant acidosis. However, there continued to be a significant risk of hypotension associated with serum ionised calcium < 1.02 mmol/L even when arterial pH was added to the multivariate model (hazard ratio 1.6; 95% CI 1.2-2.2; $p = 0.002$). There was no significant difference in the risk of hypotension for patients randomised to intensive versus less CRRT, according to quartiles of CRRT ultrafiltration rate and CRRT blood flow rate, nor with citrate versus non-citrate CRRT anti-coagulation.

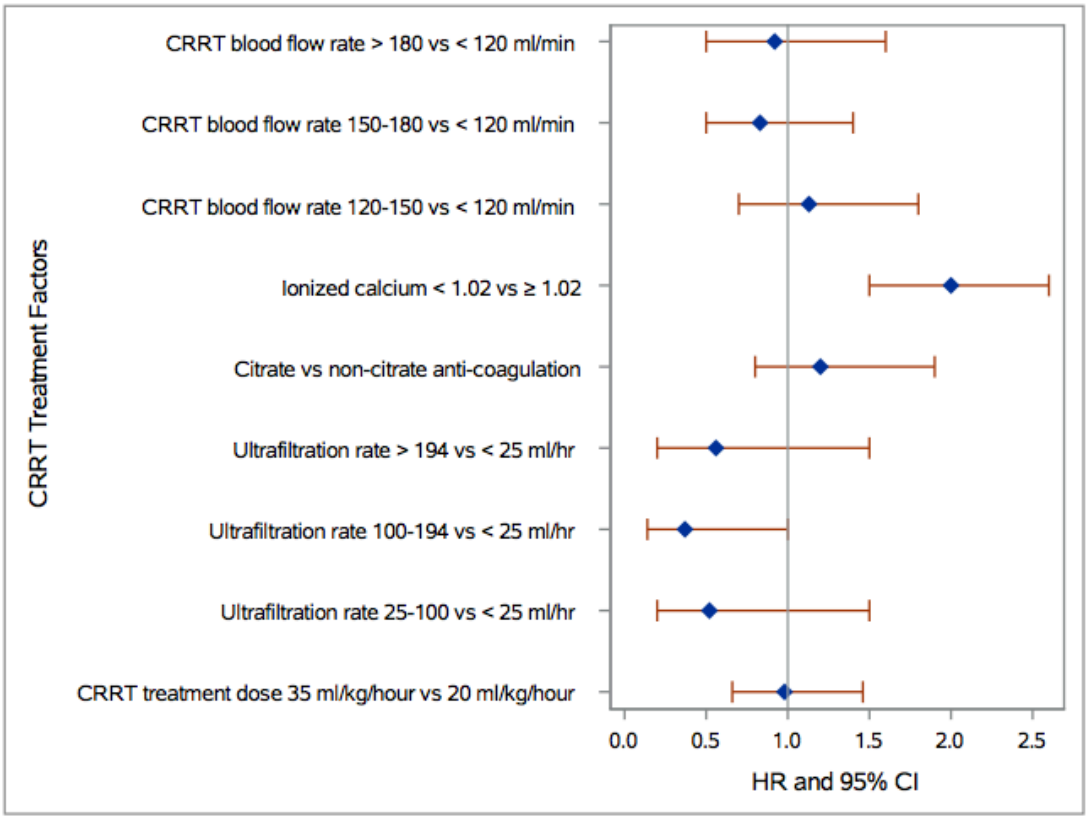
Table 3.5: Cox proportional sub-distribution hazards model for hazard of experiencing hypotensive events on CRRT according to CRRT treatment factors. Results reported as hazard ratios (95% confidence interval).

Treatment factor	Univariate HR	Univariate P-value	Model 1 HR*	Model 1 P-value	Model 2 HR**	Model 2 P-value
Intensive vs less intensive CRRT treatment dose	0.77 (0.58-1.02)	0.07	0.75 (0.57-0.99)	0.05	0.98 (0.66-1.46)	0.92
Ultrafiltration rate 25-100 ml/hour	0.9 (0.54-1.48)	0.67	0.85 (0.5-1.4)	0.53	0.52 (0.2-1.5)	0.21
Ultrafiltration rate 100-194 ml/hour	0.93 (0.56-1.53)	0.77	0.86 (0.5-1.4)	0.56	0.37 (0.14-1.00)	0.05
Ultrafiltration rate > 194 ml/hour	1.5 (0.9-2.5)	0.12	1.38 (0.8-2.3)	0.21	0.56 (0.2-1.5)	0.26
Citrate anticoagulation	1.16 (0.9-1.6)	0.35	1.13 (0.8-1.5)	0.42	1.2 (0.8-1.9)	0.43
Ionised calcium < 1.02 mmol/L	2.8 (2.2-3.7)	< 0.0001	2.7 (2.1-3.5)	< 0.0001	2.0 (1.5-2.6)	< 0.0001
CRRT blood flow rate 120-150 ml/min	1.01 (0.7-1.4)	0.97	1.02 (0.74-1.4)	0.93	1.13 (0.7-1.8)	0.61
CRRT blood flow rate 150-180 ml/min	0.78 (0.6-1.1)	0.17	0.85 (0.6-1.2)	0.36	0.83 (0.5-1.4)	0.46
CRRT blood flow rate > 180 ml/min	1.07 (0.8-1.5)	0.69	1.11 (0.8-1.6)	0.56	0.92 (0.5-1.6)	0.75

*Model 1 = treatment factor, hospital length of stay pre randomisation, ICU length of stay pre randomisation, study site, baseline VIS.

**Model 2 = treatment factor, hospital length of stay pre randomisation, ICU length of stay pre randomisation, study site, baseline VIS, mechanical ventilation, baseline APACHE II score, baseline total SOFA score, baseline Cleveland Clinic Acute Renal Failure score, oliguria, age, sepsis, chronic hypoxaemia, PA systolic pressure.

Figure 3.2: Forest plot of odds ratios for the association of CRRT treatment factors with risk of severe hypotension during the trial



3.5 Discussion

In this post-hoc analysis of the ATN trial, 59.8% patients experienced severe hypotension while being treated with continuous renal replacement therapy. The majority of these events occurred on the first two days of treatment. In a multivariable adjusted model, a serum ionised calcium < 1.02 mmol/L was associated with a significant increase in the risk of treatment-associated hypotension, while CRRT treatment intensity, type of anti-coagulation used and CRRT blood flow rate did not have a significant effect on the risk of CRRT-associated hypotension, when analysed according to CRRT treatment days only.

Higher intensity CRRT (> 35 ml/kg/hour) has not been shown to decrease mortality in several randomised controlled trials (VA/NIH Acute Renal Failure Trial Network., 2008; RENAL Replacement Therapy Study Investigators., 2009; Park., 2016) but has been associated with adverse effects including hypophosphatemia, essential nutrient loss and removal of important medications including antibiotics (Umber., 2014; Lewis., 2014). Despite

this, high intensity CRRT is still frequently prescribed in international surveys, particularly for patients with sepsis and acidaemia (Clark., 2017; Cottle., 2016; Legrand., 2013; Guo., 2017). A recent meta-analysis which merged individual patient data from randomised controlled trials comparing high versus standard intensity RRT in intensive care patients with severe AKI found that higher intensity RRT did not affect mortality, but did appear to delay renal recovery, with a longer time to cessation of RRT through 28 days (Wang., 2018).

Similarly, in a secondary analysis of the ATN trial limited to patients who were treated solely with intermittent haemodialysis, investigators found that the odds of renal recovery by 28 days were significantly lower for those who were treated with intensive haemodialysis (6 treatments per week) compared to those who were treated with less intensive haemodialysis (3 treatments per week, despite achieving higher net ultrafiltration per treatment in the patients who were treated with lower intensity haemodialysis (Vijayan., 2018). The rates of intradialytic hypotension per treatment were similar for both groups, resulting in a greater number of treatments complicated by intradialytic hypotension in the high intensity haemodialysis strategy. The authors hypothesised that intradialytic hypotension could have resulted in recurrent renal ischaemia, which has been shown to delay recovery of renal function (McCausland., 2016; Conger., 1990; Solez., 1979).

In our secondary analysis of the ATN trial, we found that, while more than half of patients who receive CRRT experience severe hypotension while on treatment, there was no significant difference between intensive and less intensive CRRT groups with regard to the incidence of treatment-associated hypotension. Treatment dose therefore does not seem to be a significant risk factor for determining the rate of haemodynamic complications for CRRT patients. From our baseline demographic data we can see that illness severity scores such as APACHE II and SOFA, along with markers for organ failure including mechanical ventilation and oliguria, act as much more reliable predictors for who is more likely to experience hemodynamic instability on CRRT,

Other modifiable CRRT treatment factors have, however, been found to affect the risk of morbidity and mortality in the ICU. A post-hoc secondary analysis of the ATN trial assessed the risk of mortality and renal recovery according to tertiles of ionised calcium during the trial and found that severe hypocalcaemia independently predicted mortality in patients with AKI

requiring RRT, though there was no significant effect on renal recovery and hospital/ICU length of stay (Afshinnia., 2013). We found that a serum ionised calcium < 1.02 mmol/L was associated with a significantly increased risk of treatment-associated hypotension, in keeping with other studies of patients with AKI requiring RRT and highlighting the need to monitor for and control hypocalcaemia associated both with AKI and with RRT treatment strategies.

Mixed results have been seen for the impact of net ultrafiltration on mortality in the ICU. Murugan et al selected patients with fluid overload ≥ 5% body weight from a large academic centre ICU dataset and found that net ultrafiltration > 25 ml/kg/day was associated with lower 1-year risk-adjusted mortality compared to net ultrafiltration ≤ 20 ml/kg/day (Murugan., 2018). However, a subsequent secondary analysis of the Randomized Evaluation of Normal versus Augmented Level of Renal Replacement Therapy (RENAL) trial conversely found that net ultrafiltration rates > 1.75 ml/kg/hour were associated with significantly lower survival compared to net ultrafiltration rates < 1.01 ml/kg/hour (Murugan., 2019).

A recently published retrospective analysis by Tehranian et al from the Mayo Clinic may help to explain this dichotomy as it seems to indicate that when adjusted for markers of increased volume status, there is no longer a haemodynamic benefit to increasing rates of ultrafiltration; i.e. that potential haemodynamic benefits associated with increased UF are experienced only by patients who are significantly volume overloaded in a manner that may cause haemodynamic compromise (Tehranian., 2019). However, we did not note any change in risk of hypotension associated with ultrafiltration rate in our multivariate adjusted model in this secondary analysis. We used a stepwise incremental approach to building our final multivariate model, including multiple illness severity scores (the APACHE II, SOFA and Cleveland Clinic Acute Renal Failure scores) as these differed significantly at baseline between the patients who did or did not subsequently develop hypotension in the trial. We did not find any statistical evidence of collinearity between the different illness severity scores used in our final multivariate model.

The major strength of our study is the use of a large, randomised controlled trial of two different RRT strategies, which predictably leads to differences in small solute clearance between the two arms. Using treatment assignment as the primary exposure of interest, we were able to circumvent the possibility of confounding by other factors related to hemodynamic

instability for critically ill patients. We also used a relatively high cut-off VIS value for adjudication of severe hypotension and therefore minimised the risk of false positive associations between CRRT treatment factors and treatment-associated hypotension as a result of this.

Our study has several important limitations. Although the data were generated from 27 centres, recruitment was predominantly in tertiary-care academic medical centres and Veterans Administration hospitals, limiting generalisability. Even though this is a secondary analysis of a well-designed clinical trial, it was not primarily designed to assess the effect of intensity of CRRT on haemodynamic outcomes. As a consequence, haemodynamic outcomes were not measured uniformly or consistently for all participants; in particular, echocardiographic measurements including right and left ventricular function were not recorded. We therefore cannot infer to what extent cardiogenic shock may have influenced the incidence of severe hypotension for patients in this trial. It was not possible to measure accurate time to hypotensive events as these were only recorded on a daily basis, and not on a more precise hourly basis.

3.6 Conclusions

In our secondary analysis of the ATN trial, neither intensive CRRT nor ultrafiltration rate were not associated with an increased risk of severe hypotension. Hypocalcaemia with a serum ionised calcium < 1.02 mmol/L was associated with a significantly increased risk of treatment-associated hypotension. Further studies will be required to assess whether strict treatment targets for management of hypocalcaemia on CRRT will help to improve the risk of CRRT-associated hypotension in the future.

CHAPTER 4

Higher plasma KIM-1 is associated with increased 28-day mortality and decreased renal recovery in patients with severe AKI requiring renal replacement therapy

4.1 Abstract

Introduction: Plasma kidney injury molecule-1 (KIM-1), a protein synthesised by renal proximal tubular cells, increases during periods of ischaemia, and as a result acts as a sensitive marker for AKI severity. We hypothesised that higher plasma KIM-1 levels assessed prior to commencing renal replacement therapy (RRT) would associate with higher mortality and RRT dependence in critically ill patients with severe AKI.

Methods: We measured plasma KIM-1 levels in 806 Day 0 and 417 Day 8 samples from participants in Acute Renal Failure Trial Network (ATN) trial, a randomised controlled trial of intensive versus less-intensive RRT. For our primary analysis we used a logistic regression model to assess the risk of 28-day mortality and an inverse probability weighted logistic regression model to assess the odds of 28-day renal recovery, according to log-transformed Day 0 KIM-1.

Results: Higher levels of plasma KIM-1 measured at day 0 were associated with an increased risk of death within 28 days (adjusted odds ratio 1.23; 95% CI 1.04-1.45). Higher levels of day 0 plasma KIM-1 were also associated with an increased risk of persistent RRT dependence at 28 days (adjusted odds ratio 0.67; 95% CI 0.52-0.86) per 1 unit increase in log-transformed plasma KIM-1.

Conclusions: Higher plasma KIM-1 levels assessed prior to initiation of RRT are independently associated with increased 28-day mortality and decreased 28-day renal recovery in critically ill patients with severe AKI.

4.2 Introduction

Acute kidney injury (AKI) complicates 20% of inpatient admissions and 30-50% of intensive care unit (ICU) admissions (Star., 1998). Attributed costs of AKI in the United States are estimated at $10 billion annually (Vandijck., 2007). Despite decades of research, renal replacement therapy (RRT), in the form of intermittent haemodialysis (IHD) or continuous renal replacement therapy (CRRT), remains the primary therapy to treat severe AKI and its complications.

Kidney-specific biomarkers have been localised to specific areas or functions within the nephron and can potentially help to characterize glomerular, tubular or interstitial injury; inflammation; or repair (Menez., 2019). Kidney injury molecule 1 (KIM-1) is a transmembrane glycoprotein whose ectodomain is cleaved by matrix metalloproteinases and is present in the urine of humans and rodents after kidney proximal tubular injury (Han., 2002). It is up-regulated more than any other protein in the renal proximal tubules in the setting of AKI (Bonventre., 2009), and has important anti-inflammatory properties as part of the innate immune response, including phagocytosing apoptotic cells (Yang., 2015). Plasma KIM-1 increases during periods of renal ischemia and can act as a sensitive marker for AKI severity (Sabbisetti., 2014). We hypothesised that higher baseline plasma KIM-1 levels prior to commencing RRT would be associated with increased mortality and decreased renal recovery in critically ill patients with severe AKI.

To test our hypotheses, we measured plasma KIM-1 levels in day 0 samples from participants in the Acute Renal Failure Trial Network (ATN) trial, a randomised controlled trial of intensive versus less-intensive RRT for patients with severe AKI (VA/NIH Acute Renal Failure Trial Network., 2008). We hypothesised that mortality is significantly higher and that renal recovery is significantly lower per 1 unit increase in log-transformed plasma KIM-1.

4.3 Methods

4.3.1 Study design and population

The ATN trial was a multicentre randomised controlled trial performed at 27 VA and university-affiliated health centres between November 2003 and July 2007 in which 1124 patients with severe acute kidney failure were assigned to RRT at two different intensities (VA/NIH Acute Renal Failure Trial Network., 2008). Patients were eligible if they had AKI requiring RRT and failure of at least one non-renal organ (defined as a non-renal Sequential Organ Failure Assessment Score of two or more) or sepsis. Additional inclusion and exclusion criteria are described elsewhere in detail (VA/NIH Acute Renal Failure Trial Network., 2008). In the group receiving the intensive-therapy strategy, intermittent haemodialysis and sustained low-efficiency dialysis (SLED) were provided six times per week and continuous venovenous haemodiafiltration was prescribed to provide a total effluent flow rate of 35 ml per kilogram of body weight per hour. In the less-intensive strategy, intermittent haemodialysis and sustained low-efficiency dialysis were provided three times per week and continuous venovenous haemodiafiltration was prescribed to provide a total effluent flow rate of 20 ml per kilogram per hour. The use of IHD or CRRT was based on haemodynamic stability. Assigned interventions were delivered for up to 28 days after randomisation or until renal recovery, discharge from the ICU, withdrawal of care, or death.

Subject enrolment began in November 2003 and was completed in July 2007. At the time of randomisation (day 0), blood samples (n = 817) were obtained in EDTA-containing vacutainers, immediately placed on ice, centrifuged at 4 degrees Celsius and the plasma was aliquoted and stored in a biorepository at -80 degrees Celsius. Additional samples (n = 556) were collected and stored 1 week later (day 8) for patients who were still alive. We measured plasma KIM-1 using available samples from the biorepository (n = 806 from day 0).

4.3.2 Exposures and Outcomes

We obtained de-identified data from the National Institute of Diabetes and Digestive and Kidney Diseases ATN study data repository. The study protocol was approved by the Partners Institutional Review Board. Demographic data (age, gender, race), co-morbid data (high blood pressure, diabetes, malignancy, Sequential Organ Failure Assessment [SOFA]

score, congestive heart failure, previous myocardial infarction, chronic hypoxaemia) along with weight were recorded at baseline for all study participants. The primary exposure of interest was baseline (day 0) plasma KIM-1, taken prior to initiation of RRT. The primary outcome measures were mortality and renal recovery at day 28. Renal recovery was defined by the ATN trial investigators as lack of need for continuing dialysis support at the time of study completion (day 28) or at death. The trial investigators used day 28 as a cut-off point for determining renal recovery based on prior clinical evidence that the majority of patients who recover kidney function following AKI do so in the first four weeks (Schiffl., 2002; Ronco., 2000; Mehta., 2001).

4.3.3 KIM-1 measurement

The ATN trial stored plasma biosamples in 817 out of 1124 patients. Characteristics of the patients who provided samples were similar to the overall cohort (Supplemental Table 1). These samples have been stored at -80C and were used in previous studies from our research group (Leaf., 2018; Leaf., 2019) and others (Srisawat., 2011; Pike., 2015). Our data indicate that KIM-1 is stable for up to at least 5 freeze-thaw cycles. Microbead-based assays for human plasma KIM-1 were developed by our laboratory research group and extensive validation of the assays was performed using previously described approaches (Sabbisetti., 2014; Leaf., 2019., Vaidya 2008). AF1750 capture antibodies (R&D Systems) for human plasma samples were conjugated with COOH polystyrene beads (Bio-Rad) and incubated with 30 µl of sample or recombinant KIM-1 protein (1750-TM for humans, R&D systems) for 60 minutes. After incubation, beads were washed and incubated with biotinylated anti-KIM-1 detection antibody (BAF 1750 for humans, R&D systems) for 45 minutes. Beads were washed again and incubated for 15 minutes with the streptavidin-phycoerythrin solution (Invitrogen). The signal from the fluorochrome, which is directly proportional to the amount of antigen bound at microbead surface, was measured using Luminex 200. The upper and lower end of detection of our standard curve were 20000 pg/ml and 27.4 pg/ml, respectively. The observed concentration coefficients of variation were between 0-20%.

4.3.4 Statistical analysis

Scatterplots were used to graphically display log-transformed KIM-1 levels. Continuous variables were examined graphically and recorded as means (+/- SDs) for normally distributed data or medians (with IQRs) for non-normally distributed data. Comparisons were made using t-tests or Wilcoxon rank sum tests as appropriate. Categorical variables were analysed by chi-square testing. The primary outcomes were 28-day mortality and 28-day renal recovery according to log-transformed baseline KIM-1 measurement.

For our primary analysis we used a logistic regression model to assess the risk of 28-day mortality according to log2-transformed day 0 KIM-1 and an inverse-weighted probability logistic regression model (weighted for the competing risk of death) to assess the risk of 28-day renal recovery according to log2-transformed day 0 KIM-1. In order to determine whether risk prediction models for 28-day mortality and renal recovery were improved by the addition of log2KIM-1, we calculated the Harrell C-index for a model containing components of the ATN mortality risk score, baseline total SOFA score, age-adjusted Charlson score and Cleveland Clinic Acute Renal Failure score. We then added log2KIM-1 to examine the change in C-index. All models were implemented in SAS (SAS Institute Inc., Cary, NC) using PROC LOGISTIC. A two-tailed p value < 0.05 was considered evidence of statistical significance for all outcomes.

4.4 Results

4.4.1 Baseline demographic, illness severity and biochemical data according to D0 KIM-1 quartiles

We measured day 0 KIM-1 in 806 available plasma samples from 1124 subjects in the ATN trial. Day 0 KIM-1 was divided into quartiles in order to compare baseline patient characteristics between these groups (Table 4.1). Younger patients had significantly higher day 0 KIM-1 levels. Patients with lower baseline KIM-1 levels had higher age-adjusted Charlson comorbidity index scores; specifically those in Quartile 1 had significantly higher age-adjusted Charlson comorbidity index scores compared to those in Quartile 4 when a Bonferroni correction was applied. However, patients with higher baseline KIM-1 levels had

higher baseline total-SOFA scores and Cleveland Clinic ICU Acute Renal Failure scores. When a Bonferroni correction was applied for multiple comparisons, patients in Quartile 4 had significantly higher baseline total-SOFA scores than those in Quartile 1 and 2, but not those in Quartile 3. Similarly, patients in Quartile 4 had significantly higher baseline Cleveland Clinic ICU Acute Renal Failure scores than those in Quartile 1, but not those in Quartile 2 or 3. There was a weak monotonic non-linear correlation between day 0 KIM-1 and Day 0 serum creatinine (Spearman correlation coefficient 0.15; p = 0.000; Figure 4.1).

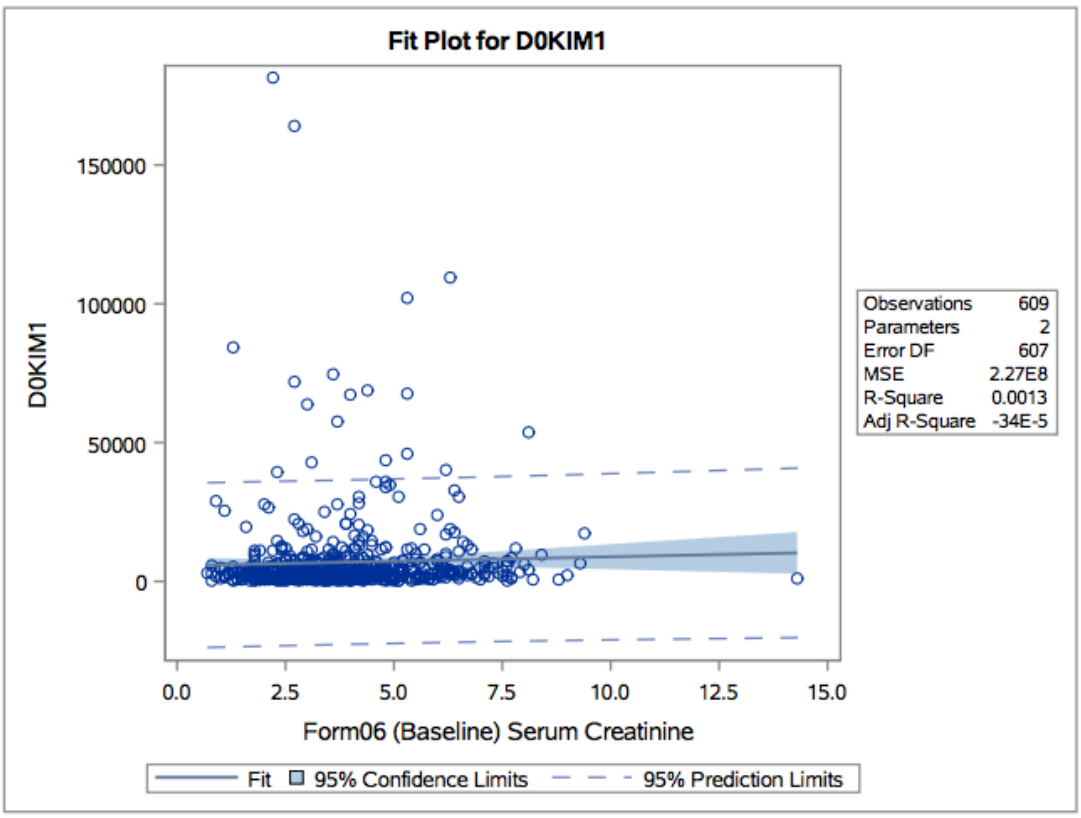
Table 4.1: Baseline demographic, illness severity and biochemical data according to baseline KIM-1 quartile

Day 0 KIM-1 (pg/ml)	**Quartile 1 (**0-1393.8)	**Quartile 2 (**1393.8-2890.3)	**Quartile 3** (2890.3-5993)	**Quartile 4** (5993-181509.6)	**P-value**
Age	64 +/- 15*	61.3 +/- 13.8*	59.6 +/- 15.4*	54.8 +/- 16.1	< 0.0001
Sex (no./no. with data)					
Male	105/153 (68.6%)	109/152 (71.7%)	101/152 (66.5%)	101/152 (66.5%)	0.73
Female	48/153 (31.4%)	43/152 (28.3%)	51/152 (33.6%)	51/152 (33.6%)	
Race (no./no. with data)					
White	118/153 (77.1%)	120/152 (79%)	115/152 (75.7%)	118/152 (77.6%)	0.87
Black	24/153 (15.7%)	20/152 (13.2%)	25/152 (16.5%)	24/152 (15.8%)	
Hispanic	7/153 (4.6%)	10/152 (6.6%)	10/152 (6.6%)	8/152 (5.3%)	
Other	4/153 (2.6%)	2/152 (1.3%)	2/152 (1.3%)	2/152 (1.3%)	
Renal function before onset of acute kidney injury/at randomization					
Premorbid serum creatinine – mg/dl	1.17 +/- 0.34	1.1 +/- 0.36	1.16 +/- 0.8	1.02 +/- 0.3	0.06
Serum creatinine at randomisation – mg/dl	3.9 +/- 2.5	4.0 +/- 1.8	3.9 +/- 1.8	4.5 +/- 1.8	0.08
Cause of acute kidney injury (no./no. with data)					
Ischemia	113/141 (80.1%)	118/145 (81.4%)	125/148 (84.5%)	121/145 (83.5%)	0.77
Nephrotoxins	34/135 (25.2%)	50/139 (36%)	37/140 (26.4%)	38/138 (27.5%)	0.18
Sepsis	72/141 (51.1%)	82/142 (57.8%)	79/144 (54.9%)	86/142 (60.6%)	0.42
Multifactorial	72/141 (51.1%)	92/145 (63.5%)	86/144 (59.7%)	88/144 (61.1%)	0.16
Weight before acute illness - kg	84.1 +/- 18	82.7 +/- 18.3	82.3 +/- 19.6	84.9 +/- 20.3	0.63
Length of stay before randomisation - days					
Hospital	8.5 +/- 7.7	10.4 +/- 17.6	12.7 +/- 27.4	13.8 +/- 18.6	0.06
ICU	6.1 +/- 5.7	8.3 +/- 13.4	6.6 +/- 5.8	5.9 +/- 6.1	0.06

Illness severity score					
Charlson comorbidity index	2.8 +/- 2.3	3.0 +/- 3.3	2.3 +/- 2.0	2.5 +/- 2.4	0.15
Age-adjusted Charlson comorbidity index	4.9 +/- 2.7*	4.7 +/- 3.6	4.1 +/- 2.4	3.8 +/- 2.8	0.005
Mechanical ventilation (no./no. with data)	120/153 (78.4%)	122/152 (80.3%)	132/152 (86.8%)	119/152 (78.3%)	0.19
APACHE II score	26 +/- 7	26.1 +/- 7.7	26.7 +/- 6.5	26.3 +/- 7.2	0.85
Total SOFA score	13.6 +/- 3.7*	13.6 +/- 3.7*	15.5 +/- 3.6	15.3 +/- 3.4	< 0.0001
Cleveland Clinic ICU Acute Renal Failure Score	10.9 +/- 3.5*	11.5 +/- 3.4	12.6 +/- 3.1	12.6 +/- 3.3	< 0.0001
Oliguria (no./no. with data)	122/153 (79.7%)	116/152 (76.3%)	129/152 (84.9%)	124/152 (81.6%)	0.3
Median D8 KIM-1 (IQR) – pg/ml	1008.1 (677.7-1331.8)*	1963.2 (1658.2-2421.1)*	4347.1 (3540.3-5207.7)*	10947.5 (7170.2-18426.8)	< 0.0001

Data expressed as means +/- standard deviation unless otherwise stated.
**P < 0.05 in pairwise comparisons with Quartile 4 when Bonferroni correction applied for multiple comparisons between means.*

Figure 4.1: No linear correlation between day 0 plasma KIM-1 and day 0 serum creatinine



4.4.2 Risk of mortality by day 28 according to day 0 KIM-1

The median day 0 KIM-1 level for patients who survived to day 28 was 2679 (1315.3-5494.5) pg/ml, compared to 3148.1 (1588.5-6672.5) pg/ml for patients who did not survive to day 28 ($p = 0.03$). The median day 0 KIM-1 level for patients who survived to day 28 and recovered renal function was 1880.6 (1054.4-4646.5) pg/ml compared to 3160.6 (1617.1-6612.2) pg/ml for those who survived to day 28 but remained RRT dependent ($p = 0.007$ by Kruskal-Wallis test; Figure 2). The median day 0 KIM-1 level for patients who died before day 28 but who recovered renal function was 2348.9 (1300.5-4582.1) pg/ml compared to 3099 (1369.1-7056.8) pg/ml for patients who died before day 28 and remained RRT-dependent at the time of death (Figure 4.2).

Using a logistic regression model, there was a significantly higher risk of 28-day mortality for patients with day 0 KIM-1 levels in Quartile 4 compared to Quartile 1 (odds ratio

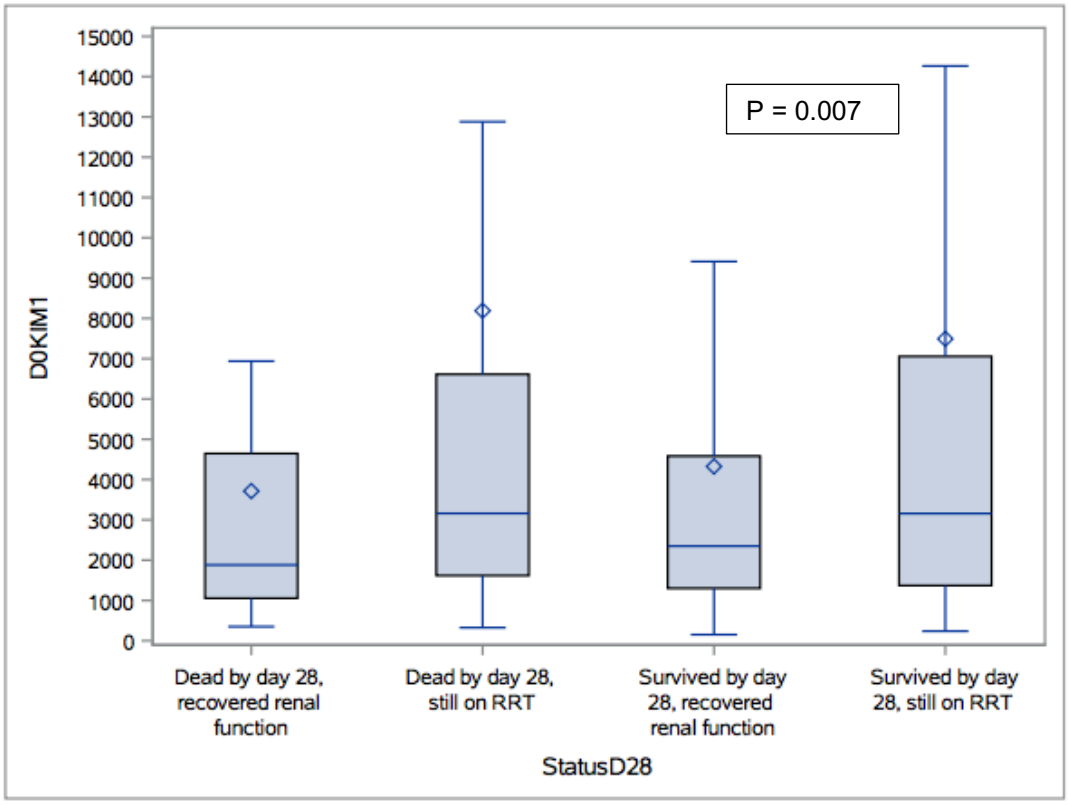
1.6, 95% CI 1.01-2.5; Table 4.2; Figure 4.2). There was also a significantly higher risk of 28-day mortality for patients with D0 KIM-1 levels in Quartile 4 compared to Quartile 1 in a multivariate model adjusted for components of the ATN trial mortality risk score (age, chronic hypoxaemia, CVS disease, malignancy, immunosuppressive therapy, ischemic AKI, post open surgery, heart rate at RRT initiation, mean arterial pressure at RRT initiation and urine volume at RRT initiation) (odds ratio 1.9; 95% CI 1.1-3.3). However, there was no significant difference in risk of 28-day mortality for patients with day 0 KIM-1 levels in Quartile 2 or 3 compared to Quartile 1. When day 0 KIM-1 was log-transformed, there was a significantly higher risk of 28-day mortality according to logKIM-1; both in univariate (odds ratio 1.19; 95% CI 1.03-1.37) and multivariate analysis (odds ratio 1.23; 95% CI 1.04-1.45). Similarly, there was a significantly higher risk of 28-day mortality according to doubling in logKIM-1; both in univariate (odds ratio 1.13; 95% CI 1.02-1.24) and multivariate analysis (odds ratio 1.15; 95% CI 1.03-1.29).

Table 4.2: Risk of death according to baseline plasma KIM-1

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Per log KIM-1	Per log2 KIM-1
Model 1	Ref	1.32 (0.83-2.1)	1.43 (0.9-2.3)	1.6 (1.01-2.5)	1.19 (1.03-1.37)	1.13 (1.02-1.24)
Model 2	Ref	1.02 (0.53-2.0)	0.62 (0.31-1.23)	1.24 (0.64-2.4)	1.15 (0.94-1.4)	1.1 (0.96-1.3)
Model 3	Ref	1.43 (0.84-2.46)	1.51 (0.89-2.57)	1.9 (1.1-3.3)	1.23 (1.04-1.45)	1.15 (1.03-1.29)

Model 1: Unadjusted analysis
Model 2: Adjusted for age, baseline total SOFA score, age-adjusted Charlson comorbidity score and Cleveland Clinic ICU Acute Renal Failure score.
Model 3: Adjusted for components of the ATN trial mortality risk score (age, chronic hypoxaemia, CVS disease, malignancy, immunosuppressive therapy, ischemic AKI, post open surgery, heart rate at RRT initiation, mean arterial pressure at RRT initiation and urine volume at RRT initiation)

Figure 4.2: Box-plot of baseline KIM-1 according to day 28 mortality and renal recovery.



4.4.3 Likelihood of renal recovery by day 28 according to D0 KIM-1 quartile

The median day 0 KIM-1 levels for patients who did not recover renal function by day 28 was 3160.6 (1483.7-6756.3) pg/ml, compared to 2201.6 (1300.5-4582.1) pg/ml for patients who did recover renal function by day 28 (p = 0.0008). Using a logistic regression model for likelihood of renal recovery by day 28 according to D0 KIM-1 quartile, there was a significantly decreased likelihood of renal recovery by day 28 for patients in day 0 KIM-1 Quartile 4 compared to Quartile 1 (odds ratio 0.54, 95% CI 0.32-0.93; Table 4.3). There was also a significantly decreased likelihood of renal recovery by day 28 for patients with day 0 KIM-1 levels in Quartile 4 compared to Quartile 1 in a multivariate model adjusted for components of the ATN trial mortality risk score (odds ratio 0.39; 95% CI 0.21-0.73). There was no significant difference in the likelihood of renal recovery by day 28 for patients in day 0 KIM-1 Quartile 2 or 3 compared to Quartile 1. When we then log-transformed day 0 KIM-1 and used an inverse

probability weighted logistic regression model to account for the competing risk of death, we found that there was a significant decreased odds of renal recovery by day 28 according to logKIM-1; both in univariate analysis (odds ratio 0.74; 95% CI 0.6-0.91) and multivariate analysis (odds ratio 0.67; 95% CI 0.52-0.86). Similarly, there was a significantly decreased odds of renal recovery by day 28 according to doubling in logKIM-1; both in univariate (odds ratio 0.81; 95% CI 0.7-0.94) and multivariate analysis (odds ratio 0.75; 95% CI 0.63-0.9).

Table 4.3: Likelihood of renal recovery according to baseline KIM-1

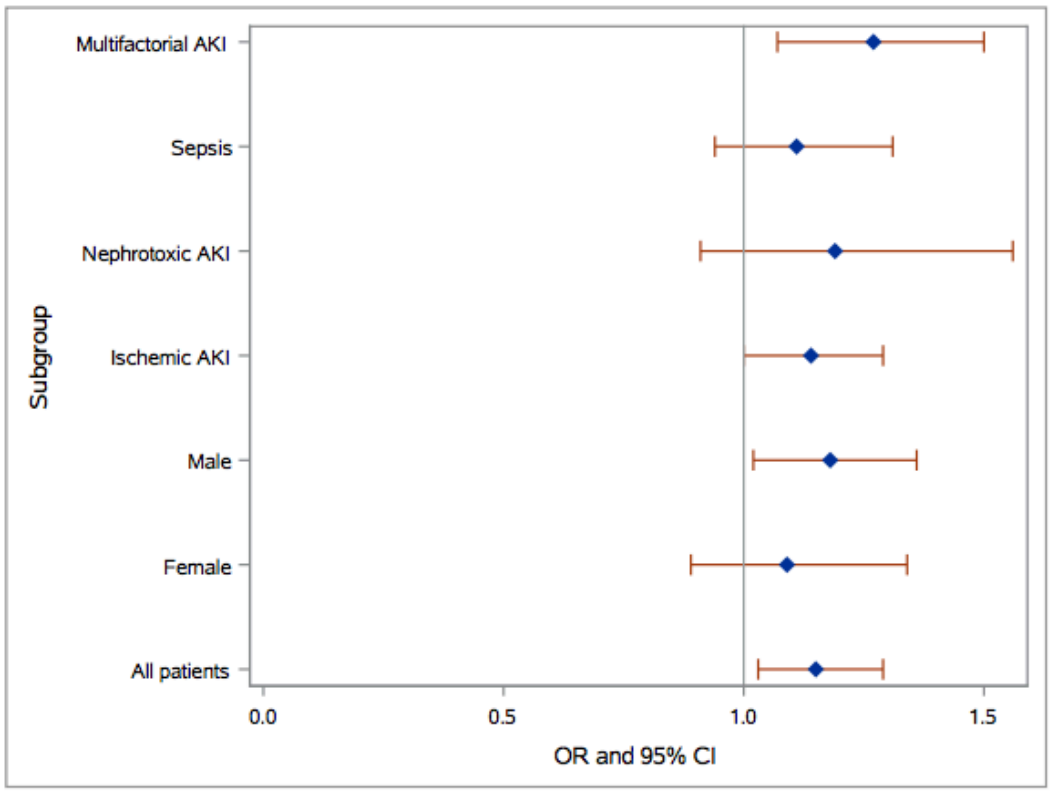
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Per log KIM-1	Per log2 KIM-1
Model 1	Ref	1.28 (0.79-2.1)	0.72 (0.43-1.2)	0.54 (0.32-0.93)	0.74 (0.6-0.91)	0.81 (0.7-0.94)
Model 2	Ref	1.14 (0.58-2.3)	0.86 (0.4-1.8)	0.43 (0.2-0.95)	0.73 (0.54-0.99)	0.8 (0.65-0.99)
Model 3	Ref	1.08 (0.6-1.9)	0.59 (0.33-1.05)	0.39 (0.21-0.73)	0.67 (0.52-0.86)	0.75 (0.63-0.9)

Model 1: Unadjusted analysis
Model 2: Adjusted for age, baseline total SOFA score, age-adjusted Charlson comorbidity score and Cleveland Clinic ICU Acute Renal Failure score.
Model 3: Adjusted for components of the ATN trial mortality risk score (age, chronic hypoxaemia, CVS disease, malignancy, immunosuppressive therapy, ischemic AKI, post open surgery, heart rate at RRT initiation, mean arterial pressure at RRT initiation and urine volume at RRT initiation)

4.4.4 Risk of mortality by day 28 according to baseline log2 KIM-1 across subgroups

We then assessed the risk of mortality by day 28 according to baseline log2 KIM-1 in different patient subgroups (sex, sepsis and cause of AKI; Figure 4.3a). There was a significantly increased risk of mortality by day 28 according to baseline log2 KIM-1 for patients who were male (odds ratio 1.18; 95% CI 1.02-1.36), who had an ischemic AKI (odds ratio 1.14; 95% CI 1.00-1.29) and who had a multifactorial AKI (odds ratio 1.27; 95% CI 1.07-1.5). There was no significant difference in risk of mortality by day 28 according to baseline log2 KIM-1 for patients who were female (odds ratio 1.09; 95% 0.89-1.34), who were septic (odds ratio 1.11; 95% CI 0.94-1.31) and who had a nephrotoxic AKI (odds ratio 1.19; 95% CI 0.91-1.56).

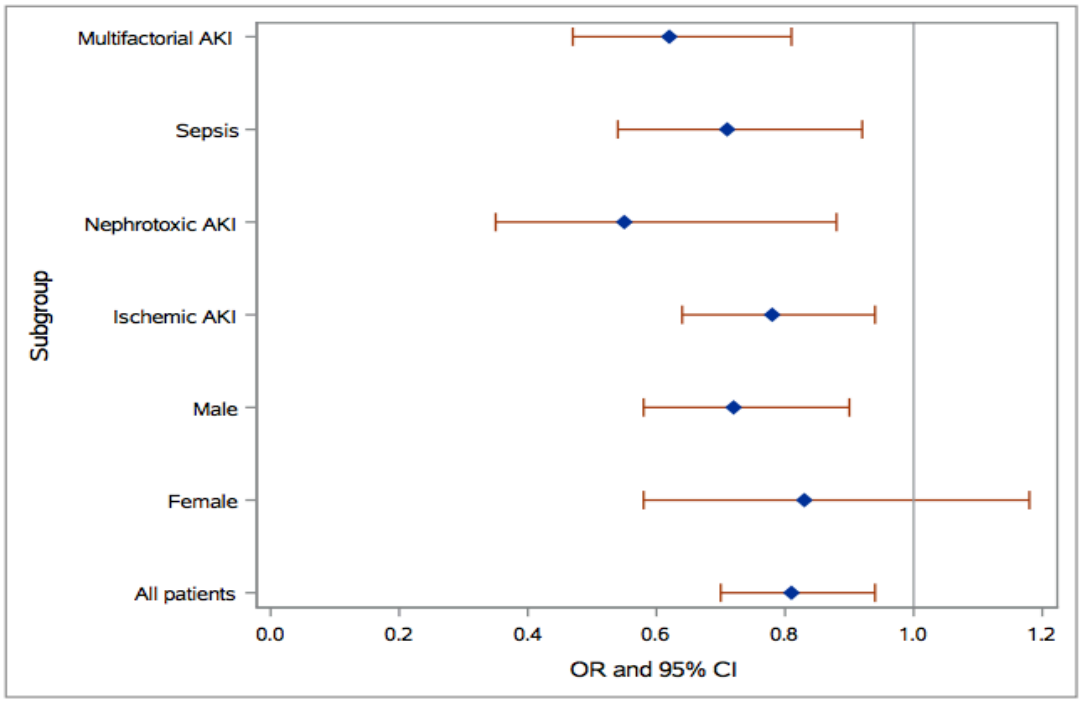
Figure 4.3a: Odds ratios for 28-day mortality according to baseline log2 KIM-1 across subgroups



4.4.5 Likelihood of renal recovery by Day 28 according to baseline log2 KIM-1 across subgroups

We also assessed the likelihood of renal recovery by day 28 according to baseline log2 KIM-1 in different patient subgroups (sex, sepsis and cause of AKI; Figure 4.3b). There was a significantly decreased likelihood of renal recovery by day 28 according to baseline log2 KIM-1 for patients who were male (odds ratio 0.72; 95% CI 0.58-0.9), who were septic (odds ratio 0.71; 95% CI 0.54-0.92), who had an ischemic AKI (odds ratio 0.78; 95% CI 0.64-0.94), a nephrotoxic AKI (odds ratio 0.55; 95% CI 0.35-0.88) or a multifactorial AKI (odds ratio 0.62; 95% CI 0.47-0.81). There was no significant difference in risk of mortality by day 28 according to baseline log2 KIM-1 for patients who were female (odds ratio 0.83; 95% CI 0.58-1.18).

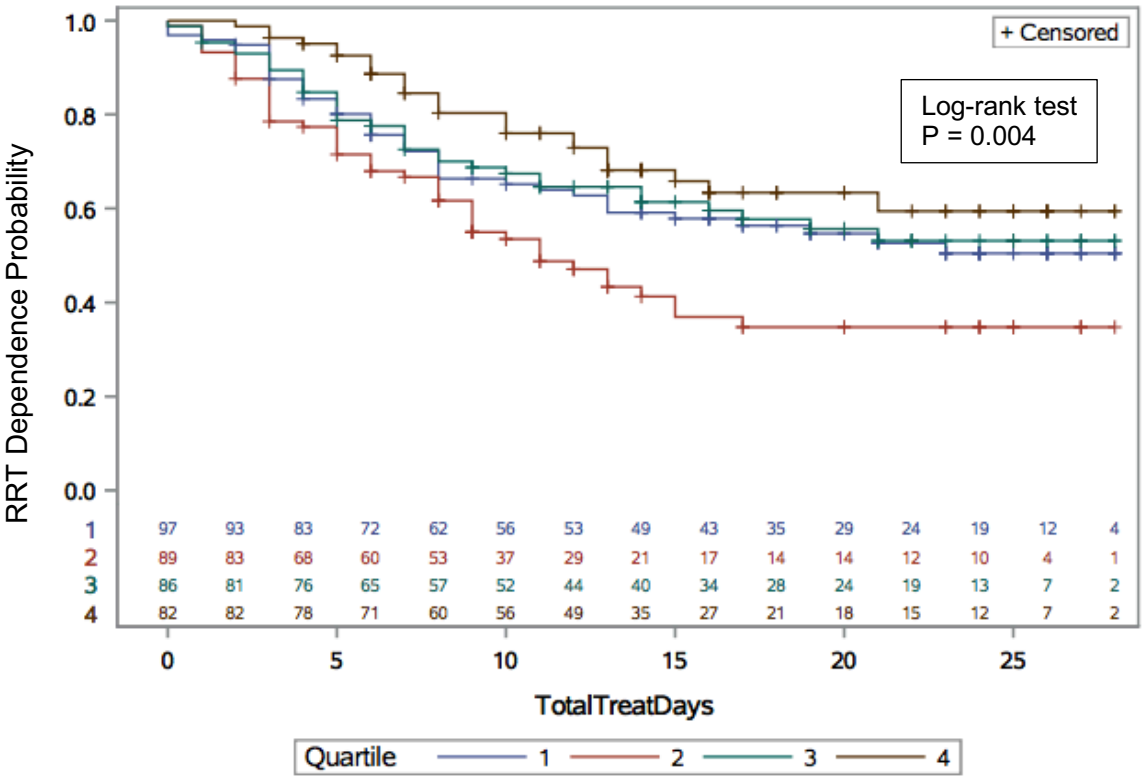
Figure 4.3b: Odds ratios for renal recovery by day 28 according to baseline log2 KIM-1 across subgroups



4.4.6 Time to independence from RRT according to day 0 KIM-1 quartile

Using Kaplan-Meier survival curves, we plotted time to independence from RRT according to day 0 KIM-1 quartile (Figure 4.4). Time to independence from RRT was significantly longer for patients with day 0 KIM-1 levels in higher quartiles compared to those with day 0 KIM-1 levels in lower quartiles (Log rank test p = 0.004). However, median number of RRT-free days (calculated as 28 – the number of RRT-dependent days; patients who died before day 28 were assigned a score of 0) did not differ significantly between the 4 quartiles (p = 0.21).

Figure 4.4: Kaplan-Meier curve of time to independence from RRT; limited to 28-day survivors only



4.4.7 Prognostic performance of plasma KIM-1 for 28-day mortality and renal recovery in patients with severe AKI requiring RRT

We examined the C-indices for prognosis of 28-day mortality and renal recovery using a base model that included components of the ATN mortality risk score (age, chronic hypoxaemia, CVS disease, malignancy, immunosuppressive therapy, ischaemic AKI, post open surgery, heart rate at RRT initiation, mean arterial pressure at RRT initiation and urine volume at RRT initiation). We then added baseline total SOFA score, age-adjusted Charlson score and Cleveland Clinic Acute Renal Failure score to the model (Table 4.4). Log2KIM-1 was then added to the final model. The C-index for 28-day mortality did not change appreciably with the addition of log2KIM-1; however the C-index for 28-day renal recovery did increase significantly from 0.73 to 0.79 with the addition of log2KIM-1 to the final model.

Table 4.4: C-index for all outcomes

Model	C-index	
	Day 28 mortality	Day 28 renal recovery
ATN mortality risk score	0.70	0.65
ATN mortality risk score + total SOFA score + age-adjusted Charlson score + Cleveland Clinic Acute Renal Failure score	0.77	0.73
ATN risk score + total SOFA score + age-adjusted Charlson score + Cleveland Clinic Acute Renal Failure score + log2KIM-1	0.80	0.79

ATN mortality risk score = age, chronic hypoxaemia, CVS disease, malignancy, immunosuppressive therapy, ischemic AKI, post open surgery, heart rate at RRT initiation, mean arterial pressure at RRT initiation and urine volume at RRT initiation

4.5 Discussion

In this secondary analysis of the ATN trial, higher levels of plasma KIM-1 measured in critically ill patients with severe AKI at the time of randomisation (day 0) to intensive versus less intensive RRT were associated with a decreased risk of 28-day renal recovery compared to lower levels of plasma KIM-1, when adjusted for components of the ATN mortality risk score in a multivariate model. Higher day 0 plasma KIM-1 levels were also associated with higher baseline eGFR, total SOFA and Cleveland Clinic Acute Renal Failure scores and with younger age.

In contrast to other AKI biomarkers, KIM-1 encoded by a gene (HAVCR) which is primarily expressed within the renal cortex; giving it greater specificity as a renal proximal tubular epithelial biomarker of ischaemic AKI (Kaplan., 1996). The majority of previous human studies have investigated urinary KIM-1 with regard to its ability to predict proximal tubular AKI and CKD progression (Han., 2002; Nielsen., 2012; Vaidya., 2011; Panduru., 2015; Waikar., 2016). Plasma AKI biomarkers may provide increased sensitivity and specificity compared to urinary AKI biomarkers as their levels in plasma are not as dependent on urine concentration effects and chronic renal insufficiency. A recent single-centre prospective study compared plasma and urinary AKI biomarkers, including KIM-1, in a cohort of patients undergoing surgery with cardiopulmonary bypass and found that plasma AKI biomarkers showed significantly better discriminative performance for pre-operative risk stratification and

early post-operative detection of AKI than urine biomarkers (Schley., 2015). This has led to increased interest in the ability of plasma KIM-1 and other plasma biomarkers to prognosticate AKI outcomes.

There is now increasing evidence for the utility of plasma KIM-1 both as a biomarker for severity of acute ischemic renal tubular injury as well as a predictor for progression of CKD. Higher levels of baseline plasma KIM-1 are have been shown to be associated with CKD progression and risk of ESRD (Schulz., 2020). Recent studies have also demonstrated that plasma KIM-1 concentrations can predict renal cell carcinoma incidence up to 5 years before diagnosis and are associated with worse survival (Scelo., 2018). A recent trial secondary analysis found that pre-angiography levels of plasma KIM-1 were significantly associated with contrast-associated AKI (Parikh., 2020). Plasma KIM-1 has also been investigated in non-renal populations and, when log-transformed, has been shown to be linearly associated with cardiovascular risk factors including blood pressure, serum cholesterol, C-reactive protein, body mass index (BMI) and smoking in healthy populations (Egli., 2018). Plasma KIM-1 has also been shown to predict progression of congestive heart failure and re-hospitalization rates for those with acute heart failure (Brankovic., 2018; Emmens., 2016). In addition to this, higher day 1 plasma KIM-1 levels have been found to be associated with higher risk of mortality and need for liver transplantation in a study of patients with acute acetaminophen-induced liver failure (Antoine., 2015).

In our secondary analysis, we have demonstrated that higher baseline plasma KIM-1 levels prior to commencement on AKI-RRT are associated with an adjusted increased risk of mortality by day 28 and a decreased risk of 28-day renal recovery for critically ill patients with severe AKI. We have also demonstrated that the addition of log2KIM-1 significantly improves risk prediction models for 28-day renal recovery. Given that higher baseline plasma KIM-1 levels are also associated with increased risk of progression to ESRD, use of plasma KIM-1 may therefore allow us to predict which patients are more likely to require long-term renal replacement therapy, and may thereby help to guide providers as part of decision-making related to long-term RRT needs. The Acute Dialysis Quality Iniative (ADQI) 10th Consensus Conference recognised the key role of novel AKI biomarkers in prognosis and management of AKI and that the appropriate next step in moving towards to clinical implementation would be

to design a multicentre randomised controlled trial in which plasma KIM-1 measurement with a pre-specified cut-off criteria for predicting reduced likelihood of renal recovery can be compared to standard of care in guiding providers about RRT decision-making and the appropriate allocation of resources for patients who are more likely to require renal support for an extended period of time (McCullough., 2013).

The major strength of our study is the use of a large, randomised controlled trial of two different RRT strategies, which predictably leads to differences in small solute clearance between the two arms, with access to a well-documented database of prospectively collected clinical, biochemical and demographic variables, as well as a large number of Day 0 plasma samples which could be used to measure KIM-1.

Our study has several important limitations. Although the data were generated from 27 centres, recruitment was predominantly in tertiary-care academic medical centres and Veterans Administration hospitals, limiting generalisability. Some of the plasma samples from the trial were missing due to depletion for previous measurements. Plasma KIM-1 was only measured at one time-point due to availability of plasma samples which was limited to day 0 of randomisation. Even though our analyses were adjusted for a large number of covariates, we cannot exclude residual confounding from unmeasured covariates.

4.6 Conclusions

In our secondary analysis of patients with severe AKI requiring RRT at two different treatment intensities in the multicentre ATN trial, higher baseline plasma KIM-1 levels prior to commencement on AKI-RRT were associated with an increased risk of 28-day mortality and a decreased risk of 28-day renal recovery for critically ill patients with severe AKI. Plasma KIM-1 measurement prior to commencement on AKI-RRT may therefore help us to prognosticate which patients are more likely to require long-term renal replacement therapy, and aid additional planning of services for patients with this ongoing need.

CHAPTER 5

Intensity of renal replacement therapy and duration of mechanical ventilation: secondary analysis of the Acute Renal Failure Trial Network Study

5.1 Abstract

Background: Randomized clinical trials have failed to show benefit from increasing intensity of renal replacement therapy (RRT), but this continues to be frequently prescribed. In addition, intensive RRT is associated with an increase in adverse events potentially secondary to small solute losses, such as phosphate. We hypothesised that, compared to less intensive RRT, intensive RRT would lead to longer duration of mechanical ventilation.

Research Question: Does intensive renal replacement therapy in critically ill patients with AKI increase time to extubation from mechanical ventilation when compared with less-intensive therapy?

Methods: The ATN study was a randomised multi-centre trial of intensive (haemodialysis or sustained low-efficiency dialysis six times per week or continuous venovenous hemodiafiltration at 35 ml/kg per hour) versus less-intensive (haemodialysis or sustained low-efficiency dialysis three times per week or continuous venovenous hemodiafiltration at 20 ml/kg per hour) RRT in critically ill patients with AKI. Of 1124 patients, 907 who were supported by mechanical ventilation on study initiation were included in this Cox proportional hazards analysis. The primary outcome was the time to first successful extubation off mechanical ventilation.

Results: Patients randomised to intensive RRT had a 33.3% lower hazard rate of successful extubation (HR 0.67, 95% CI 0.52 - 0.88, P<0.001) when compared to patients randomised to less-intensive RRT. Patients randomised to intensive RRT also had on average 2.07 ventilator-free days, compared to 3.08 days in those randomised to less-intensive RRT (P<0.001) over 14 days from start of the study.

Conclusions: Critically ill mechanically ventilated patients randomised to more intensive RRT have a longer duration of mechanical ventilation compared to those randomized to less intensive RRT. The reasons for this, such as excessive phosphate loss from more intensive RRT, deserve further study to optimise the safety and effectiveness of CRRT delivery.

5.2 Introduction

Hypophosphatemia is a frequent complication during renal replacement therapy and may contribute to poor patient outcomes due to the critical role of phosphate in energy metabolism in every organ system (Santiago., 2009; Ratanarat., 2005; Schiffl., 2013). Hypophosphatemia can impair contractile properties of the diaphragm and may impair tissue oxygen extraction by reducing intracellular 2,3 diphosphoglycerate (2,3-DPG) concentrations (Sharma., 2015). Through a post-hoc analysis of a randomised controlled trial of intensive versus less intensive RRT in critically ill patients, we sought to assess the effect of RRT treatment intensity on the duration of mechanical ventilation as a potential adverse outcome of RRT-induced phosphate depletion.

5.3 Methods

5.3.1 Statistical Analyses

We examined categorical variables by frequency distribution, recorded as proportions and made comparisons using the chi-square test. We examined continuous variables, recorded as means (SDs) or medians (IQR) using t-tests or Wilcoxon rank sum tests, as appropriate. The primary exposure of interest was the randomised treatment assignment of more-intensive vs less-intensive RRT. The primary outcome was the time to first successful extubation from mechanical ventilation in patients from study initiation through study day 14. First extubation was defined as at least 48 consecutive hours independent of ventilator support. We used a zero-inflated Poisson regression model with right censoring of data to compare ventilator-free days through Day 14 between treatment arms. Terminal extubation was not counted as an event. We calculated ventilator-free days during the first 14 days of study therapy as the days alive minus days receiving mechanical ventilation after study initiation. If a patient died, the number of ventilator-free days were the number of days between extubation and death. We performed all statistical analyses with SAS Version 9.4 (SAS Institute Inc., Cary, NC). Of note, the ATN trial did not use a specified protocol for weaning from mechanical ventilation; instead allowing the primary physicians to determine weaning management in a manner consistent with established best practices.

We used the Kaplan-Meier method to estimate survival for both treatment groups and

compared time to extubation between groups with the use of 2-sided log rank test. We estimated unadjusted hazard ratios and corresponding 2-sided 95% confidence intervals using the Cox-proportional hazards model (unadjusted model) and fit a multivariable model that was adjusted for baseline age, gender, race (black vs non-black), weight, ischaemic heart disease, congestive heart failure, chronic hypoxaemia, hypertension, diabetes, fluid balance. Subsequently, the final model was fit with the same covariates as in the multivariable model along with a pre-specified time-varying covariate of interest (cardiovascular sequential organ failure assessment score (CV SOFA scored 0-4). We used a proportional subdistribution hazards (competing risk) regression to examine the effects of treatment assignment on time to first extubation, treating death as a competing risk. We performed pre-specified subgroup analyses according to baseline tertile of serum phosphate, cause of ICU admission as well as treatment type (CRRT vs IHD) modeled as a time varying covariate. We chose baseline tertiles of serum phosphate as a pre-specified subgroup analysis in order to assess for an interaction between RRT treatment assignment and baseline serum phosphate on trial enrolment; given concern that hypophosphataemia may potentiate the effects of RRT treatment intensity on time to extubation. Unfortunately we were not able to add daily serum phosphate as a covariate to the Cox proportional hazards model as it was not measured on a consistent daily basis throughout the trial. We did however use linear mixed effect models to examine changes in subsequent serum phosphate during the study course between the two treatment arms with consideration of repeated measures. We assessed subgroup effects by testing the interaction of treatment group and subgroup treatment type and used stratified log-rank tests by treatment type to compare the randomised treatment assignment groups. We based model selection on prior clinical knowledge. A p-value of 0.05 was considered to indicate statistical significance.

5.4 Results

5.4.1 Baseline characteristics

A total of 1124 participants were randomly assigned across 27 centres to participate in the ATN study; of these 907 were on mechanical ventilation on day 1 of the study and constitute the cohort for the current analysis. The cohort had a mean age of 59 ±15.3 years and a mean weight of 84.5 ± 19 kg. The majority were men (70.4%) and 15.9% were black. 27.3% were

diabetic and 15.9% reported a known malignancy. 21% had known congestive heart failure and 10% had a history of chronic hypoxaemia. There were no significant differences between individuals randomised to intensive and less-intensive RRT (Table 5.1).

Table 5.1 - Baseline Characteristics of Study Patients who were mechanically ventilated on Day 1 according to RRT intensity randomised groups

Characteristic	**Less-intensive Strategy** No. of participants with events = 154/451	**More-Intensive Strategy** No. of participants with events = 113/456	**P value**
Mean Age, years	59.3 ± 15.3	59.3 ± 15.3	0.95
Male, %	68.5	72.3	0.21
Black, %	15.5	16.4	0.71
Mean Weight, Kg	84.2 ± 19	83.6 ± 19.5	0.67
Patients alive at 14 days, (%)	288/451 (63.8%)	293/456 (64.2%)	0.75
Hypertension, %	2.6	2.8	0.20
Diabetes, %	24.6	30	0.14
Malignancy, %	13.5	18.4	0.11
Ischemic Heart Disease, %	21.3	21.7	0.73
Congestive Heart Failure, %	21	20.6	0.80
Primary Treating service			
Medical	198/451 (43.9)	214/456 (46.9)	0.65
Surgical	201/451 (44.5)	191/456 (41.8)	
Other	52/451 (11.5)	51/456 (11.1)	
Mode of RRT on Day 1			
CVVHDF	314/388 (80.9)	313/395 (79.2)	0.14
IHD	53/388 (13.6)	61/395 (15.4)	
SLED	15/388 (3.9)	20/395 (5.0)	
Isolated Ultrafiltration	6/388 (1.5)	1/395 (0.2)	
Chronic Hypoxaemia, %	9	10.9	0.39
Cardiovascular SOFA score	3 (0-4)	3 (0-4)	1
APACHE II score	27.5 ± 7.1	28.1± 6.7	0.2
Serum Calcium (mg/dl)	7.5 ± 1.1	7.5 ± 1	0.71
Serum Creatinine (mg/dl)	3.6 ± 1.5	3.6 ± 1.5	0.72

Serum Phosphate (mg/dl)	5.4 ± 2.2	5.4 ± 2.1	1
Serum Albumin (g/dl)	2.3 ± 0.3	2.3 ± 0.4	1

5.4.2 Effect of treatment assignment on mechanical ventilation

By 14 days, there was no difference in survival between the two treatment assignments (64.3 % of patients were alive in the intensive arm as compared to 63.9% in the less-intensive arm). Patients randomised to intensive RRT had on average 2.07 ventilator-free days, compared to 3.08 days in those randomized to less-intensive RRT (P<0.001) over 14 days from start of the study. Results were similar using censor zero-inflated Poisson model (1.51 $\pm$ 0.13 fewer ventilator-free days in those randomised to intensive vs. less-intensive RRT, P < 0.001). Among the 267 patients who were successfully extubated off ventilation for at least 48 hour in the two groups, re-intubation was later performed in 19% of patients in the intensive treatment arm compared to 10% in less-intensive arm (P=0.03).

In unadjusted analyses, patients randomised to intensive RRT had a 33.3% lower hazard rate of successful extubation (HR 0.67, 95% CI 0.53 - 0.85, P<0.001) when compared to patients randomised to the less-intensive RRT (Figure 5.1). The unadjusted results were not different in the subgroup of patients with sepsis, including pulmonary infections (HR 0.62, 95% CI 0.43-0.85, P<0.001). When adjusted for baseline covariates, the effect estimate was unchanged and remained statistically significant (HR 0.67, 95% CI 0.52-0.88, P<0.001) (Table 5.2). Considering mortality as a competing risk, and using proportional sub-distribution hazards, the effect estimate was accentuated and remained statistically significant (HR 0.63, 95% CI 0.49-0.80, P<0.001).

Figure 5.1: Kaplan- Meier survival estimates for time to extubation from mechanical ventilation according to treatment intensity

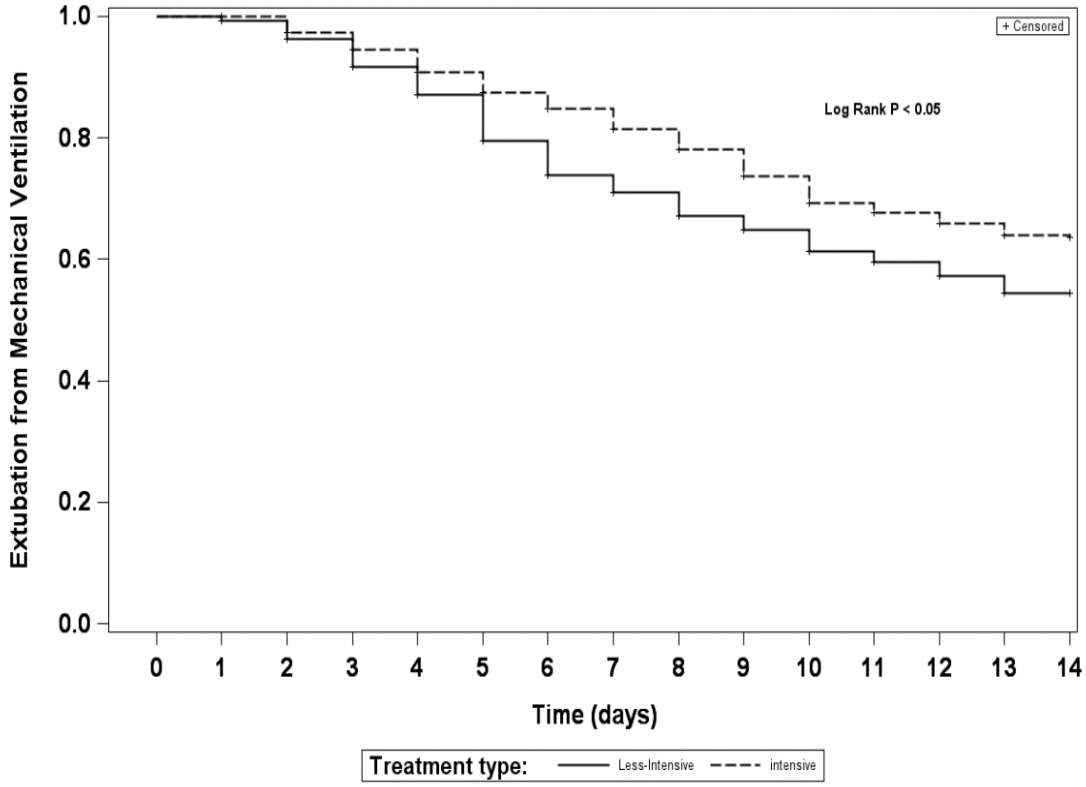


Table 5.2: Cox proportional hazards models with endpoint of first extubation from mechanical ventilation according to RRT intensity

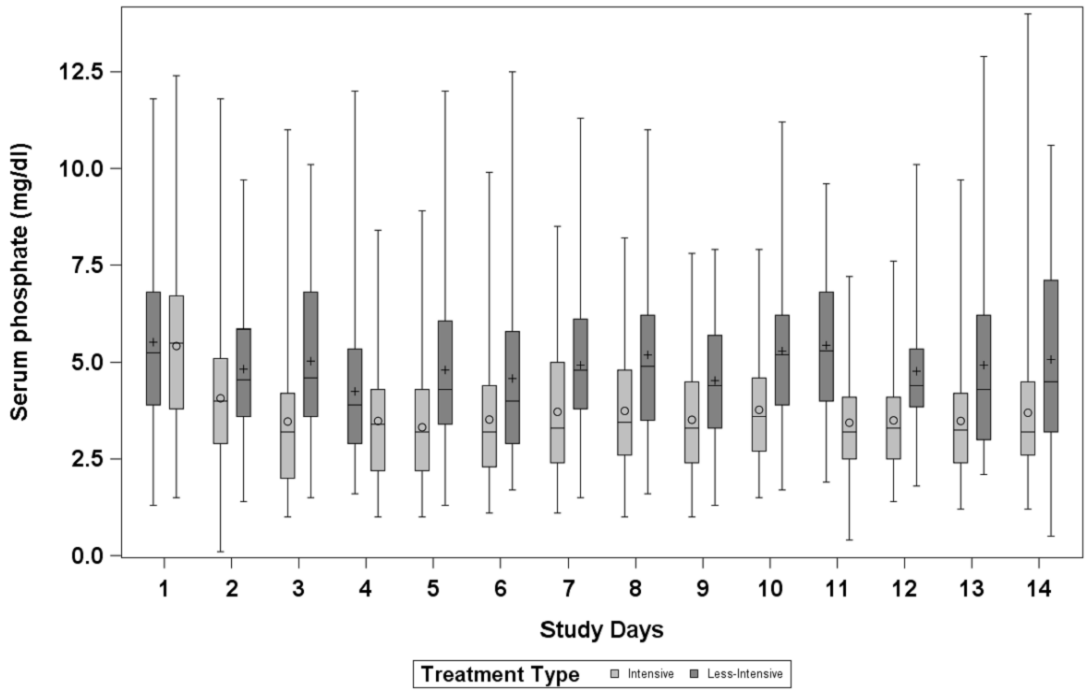
	No. of participants with events	Unadjusted Model Hazard Ratio (95% CI)	Multivariable-adjusted Model* Hazard Ratio (95% CI)
Overall study sample	267/907	0.67 (0.53-0.85)	0.67 (0.52-0.88)
Subgroup Analyses			
Sepsis	137/495	0.62 (0.43-0.86)	0.60 (0.42-0.85)
Baseline Serum Phosphate			
Tertile 1 (1.2 – 4.3 mg/dL)	87/242	0.56 (0.36-0.87; P<0.05)	0.57 (0.37-0.88; P<0.05)
Tertile 2 (4.4 – 6.3 mg/dl)	83/257	0.76 (0.49-1.1; P=0.21)	0.78 (0.5-1.2; P=0.28)
Tertile 3 (6.4 – 15.3 mg/dl)	56/244	0.71 (0.42-1.2; P=0.21)	0.65 (0.37-1.1; P=0.13)

* Multivariable-adjusted Model is adjusted for baseline age, gender, race (black vs non-black), weight, fluid balance, ischaemic heart disease, congestive heart failure, chronic hypoxemia, hypertension, diabetes and cardiovascular SOFA score.

5.4.3 Effect of treatment assignment on phosphate

Baseline serum phosphate concentrations were similar in individuals on mechanical ventilation across the two treatment arms (Table 5.1). Figure 5.2 shows the daily serum phosphate from days 1 through 14 according to randomised treatment intensity assignment. We used mixed effect models to examine changes in subsequent serum phosphate during the study course between the two treatment arms with consideration of repeated measures. There was a significantly greater reduction in serum phosphate (1.9 ± 0.1 mg/dL) in the more-intensive as compared with the less-intensive treatment group (1.0 ± 0.1 mg/dL; P <0.001). Mean nadir serum phosphate was lower in the more-intensive group compared to the less intensive group (2.6 ± 1.7 mg/dL versus 3.1 ± 1.6 mg/dL; P <0.05). 61% of patients randomized to intensive treatment had at least one hypophosphatemic event (phosphate < 2.5 mg/dL (0.81 mmol/L)) compared to 38% in the less-intensive group over 2 weeks of the study (P<0.05).

Figure 5.2: Daily phosphate concentrations from Day 1-14 according to RRT intensity (less intensive in dark and more intensive in light grey)



5.4.4 Treatment type and phosphate - Subgroup analysis

We conducted subgroup analyses according to baseline serum phosphate concentrations (Table 5.2). We found evidence of statistical interaction between randomised group and baseline phosphate tertiles (P=0.04) for the outcome of time to extubation showing presence of effect modification. Within the lowest tertile of baseline phosphate, 78% (189/242) of patients had at least one episode of hypophosphatemia during the study course. Among patients with the lowest concentrations of baseline serum phosphate (1.2 – 4.3 mg/dL), those randomised to intensive RRT had a 43% lower hazard rate of successful extubation than patients randomised to less-intensive RRT (HR 0.56, 95% CI 0.36-0.87, P<0.05). The results in the middle tertile (4.4 – 6.3 mg/dl) and highest tertile (6.4 – 15.3 mg/dl) of baseline serum phosphate were in the same direction but did not reach statistical significance, with HR 0.76 (95% CI 0.49-1.1, P= 0.21) and HR 0.71 (95% CI 0.42-1.2, P= 0.21), respectively.

We also performed analyses using treatment type (IHD, CVVHD, and SLED) as a time-dependent variable. Among patients who were on CVVHD and SLED, there was a 37.1% lower hazard rate of successful extubation (HR 0.63, 95% CI 0.42 - 0.93, P<0.05) among patients randomised to the intensive treatment arm compared to less-intensive arm. Among patients who were on IHD, there was a statistically non-significant 21.4% lower hazard rate of extubation (HR 0.78, 95% CI 0.58-1.1, P=0.12) in patients randomised to the intensive treatment arm compared to less-intensive arm.

5.5 Discussion

In this secondary analysis of a randomised controlled trial comparing strategies of more-intensive and less-intensive RRT in critically ill patients with AKI, we found that mechanically ventilated patients randomised to intensive RRT had longer duration of mechanical ventilation compared to those randomised to less-intensive RRT. Among patients who were successfully extubated initially, there was a significantly higher probability of re-intubation in those randomised to intensive RRT. Notably, during the study course, we found greater reduction in serum phosphate in the intensive treatment arm as compared with the less-intensive arm. Furthermore, within lowest baseline serum phosphate concentrations,

there was less likelihood of being extubated in the intensive RRT compared to less-intensive RRT.

There are several potential explanations for our finding that intensive RRT may increase duration of mechanical ventilation. Several iatrogenic complications associated with higher dose of RRT have been cited in RRT literature (Mueller., 2003; RENAL Replacement Therapy Study Investigators., 2009). Nutritional status is a key prognostic factor in critically ill patients with AKI. It is plausible that nutritional status is compromised by depletion of vital nutrients with increased dose RRT, particularly in continuous therapies (Finkel., 2009). Our finding that mechanical ventilation was more prolonged in those on continuous RRT rather than intermittent RRT is consistent with the hypothesis that excessive losses through continuous RRT may be the underlying reason for our observed finding.

Excessive loss of phosphate may explain our findings. Our study group at Brigham and Women's Hospital previously showed that CRRT leads to net negative phosphate balance (median -1.2 g/day, range -0.2 to - 6.5g) despite protocol driven phosphate repletion strategies if there is lack of phosphate additives in the dialysate or replacement fluids (Sharma., 2013). Excessive loss of phosphate during CVVH leading to hypophosphatemia has been reported as a complication in more than 10% of patients undergoing CRRT (Santiago., 2009; Ratanarat., 2005., RENAL Replacement Therapy Study Investigators., 2009). In the original report of the VA/NIH Acute Renal Failure Trial, hypophosphatemia was reported in 17.6% in those randomised to more-intensive RRT vs 10.9% in those randomised to less intensive RRT. Our findings, which were restricted to those on mechanical ventilation at the time of study initiation, showed similar results with a clear downward trend of phosphate over time. Although negative phosphate balance may be desirable earlier in the treatment of dialysis-requiring AKI (AKI-D), it may be detrimental to have continuous losses and negative phosphate balance during prolonged CRRT. Our findings were most pronounced in those with the lowest tertile of serum phosphate at baseline; further highlighting the importance of phosphate loss as a potential explanation of our findings.

Phosphate is the most abundant intracellular anion and is essential for multiple biological functions including nucleic acid synthesis, energy exchange, membrane transport, and intracellular signal transduction. Phosphate has been shown to have direct effects on the

diaphragm as well as effect on cellular availability of oxygen. Therefore, obligate phosphate losses may have a direct pathway for impacting pulmonary outcomes. Being primarily intracellular, phosphate orchestrates several vital enzymatic steps including a key role in red blood cell (RBC) function and oxygen transport by influencing the intracellular concentration of 2,3-DPG, a crucial allosteric effector of hemoglobin. Sharma., 2015 demonstrated that CRRT induced phosphate removal is associated with measurable reductions in RBC 2,3-DPG concentration and a corresponding shift in the oxygen hemoglobin affinity curve along with higher risk of in-hospital mortality.

Phosphate depletion is a plausible contributor to diaphragmatic and intercostal muscle weakness, which may account for our findings. Aubier., 1985 observed significant increase in trans-diaphragmatic pressure and response to phrenic nerve stimulation after correction of hypophosphatemia in 8 mechanically ventilated patients. In a prospective study of 23 patients with hypophosphatemia, Gravelyn., 1988 found respiratory muscle weakness (defined as reduction in maximal inspiratory pressure or maximal expiratory pressure) in 16 patients. In addition, the mean initial respiratory pressures were significantly lower in the hypophosphatemic group compared to the control group with normal phosphate concentrations.

Other studies have also found that hypophosphatemia may be associated with worse pulmonary outcomes. In a single-centre observational study with 321 AKI patients on continuous dialysis, Demirijian., 2011 found hypophosphatemia to be associated with higher incidence of prolonged respiratory failure requiring tracheostomy (OR 1.81; CI 1.07–3.08). In a single centre prospective cohort study of 96 intensive care patients with AKI requiring RRT, Lim., 2017 found that hypophosphatemia during RRT was independently associated with prolonged mechanical ventilation (≥7 days) (adjusted OR 14.0, 95% CI 1.37- 143.90; $P = 0.03$). The finding that hypophosphatemia was associated with poor outcomes in patients on mechanical ventilation in observational studies may be confounded by other factors such as malnutrition. A key strength of our analysis is that we used randomised treatment assignment as a proxy for unregulated solute loss.

Several studies have examined outcomes associated with hypophosphatemia outside of the context of AKI-RRT. In a retrospective analysis of 118 pediatric patients admitted to the

ICU, Kilic., 2012 found a significant difference in duration of mechanical ventilation – 7.7 days in the hypophosphatemia group compared to 4.1 days in normophosphatemia group. In addition, length of ICU stay was 9.7 days in the hypophosphatemia group compared to 5 days in the normophosphatemia group. Alsumrain., 2010 conducted a prospective analyses on 66 ICU patients and found hypophosphatemia to be associated with a 18% greater risk of failure to extubate from mechanical ventilation.

The implications of our study deserve to be highlighted, particularly given that more-intensive RRT continues to be frequently prescribed as evidenced by surveys from critical care physicians worldwide (Clark., 2017; Legrand., 2013). Intensive RRT has not been shown to improve outcomes and may, as we have shown, have deleterious effects. If our findings are from excessive losses of small solutes such as phosphate, careful monitoring and repletion strategies should be implemented.

Our study had several strengths. We assessed the outcome of time on mechanical ventilation in critically ill patients who were enrolled in a randomised controlled trial with detailed data collection on demographics, comorbid conditions, laboratory data, and clinical outcomes. The ATN study allowed us to adjust our analyses to account for number of covariates, which were evenly balanced in our post-hoc analyses, minimising residual confounding.

Our study has several important limitations. Although the data were generated from 27 centers, recruitment was predominantly in tertiary-care academic medical centers and Veterans Administration hospitals, limiting generalizability. Even though this is a secondary analysis of a well-designed clinical trial, it was not primarily designed to assess the effect of different levels of serum phosphorus during the ICU stay on the outcomes. Serum phosphorus was not measured uniformly or consistently for all participants, so we were not able to adjust for daily phosphate or test for mediation. In addition, we also lacked data on phosphorus supplementation. The ATN trial also did not consistently measure fluid balance on a daily basis therefore; though we were able to adjust for fluid balance at baseline, we were not able to adjust for this on a daily basis as a repeated measure during the trial. Similarly, markers of hypoxaemia such as the PaO2:FiO2 ratio (P/F ratio) were not measured during the trial so these also could not be added to the final multivariable model as other potential covariates for prolonged time to extubation in the more-intensive RRT treatment group. These additional fluid balance and

hypoxaemia parameters also merit further assessment as primary outcome measures in future studies of RRT treatment intensity given that they can also contribute to time to extubation from mechanical ventilation for critically ill patients.

5.6 Conclusions

Intensive RRT may lead to a greater risk of failure to extubate from mechanical ventilation, potentially from loss of small solutes such as phosphate. More aggressive repletion strategies of phosphate or other small solutes – potentially as additions to replacement or dialysate solutions - should be tested to optimise the safety and effectiveness of CRRT delivery.

CHAPTER 6

Block Randomised Implementation of a Decision-making Algorithm for Renal Replacement Therapy Initiation in Acute Kidney Injury Compared to Standard Care on AKI-related Outcomes

6.1 Abstract

Background: Acute kidney injury (AKI) requiring renal replacement therapy (RRT) is associated with high morbidity, mortality and utilisation. However, clinical decision-making related to RRT initiation for patients with AKI in the intensive care setting is not standardised.

Methods: We conducted a 12 month (July 2017-July 2018) single centre block randomized controlled trial in the intensive care units of a large academic tertiary medical centre, in which we alternated use of an AKI Standardised Clinical Assessment and Management Plan (SCAMP), a decision-making algorithm to assist front-line clinicians caring for patients with AKI, with use of a "sham" control form in 4-6 week randomisation blocks. The SCAMP algorithm provided recommendations about optimal indications for initiating RRT on the basis of various clinical parameters, whereas the sham control form did not provide any recommendations for management of AKI-RRT. Both the AKI-SCAMP and sham form captured physician-estimated treatment futility and mortality. The AKI-SCAMP also captured reasons for deviation from the recommended algorithm.

Results: 122 patients were managed with the AKI-SCAMP while 102 patients were managed with the aid of the sham control form. There was no significant difference in the primary outcome of odds of inpatient, 30-day or 60-day mortality associated with use of the AKI-SCAMP. With respect to secondary outcomes, use of the AKI-SCAMP resulted in a significantly reduced ICU length of stay (relative risk 0.68; 95% CI 0.66-0.69, $p < 0.0001$) and hospital length of stay (relative risk 0.75; 95% CI 0.72-0.79, $p < 0.0001$), as well as a reduced 30-day hospital readmission rate (odds ratio 0.38; 95% CI 0.15-0.99, $p = 0.05$). We also found that patients in the AKI-SCAMP intervention group were less likely to receive RRT despite physician-perceived treatment futility than those in the control group (1.8% vs 7.3%, $p=0.003$). Within the AKI-SCAMP arm, adherence to AKI-SCAMP recommendations resulted in a significantly reduced ICU length of stay (relative risk 0.76; 95% CI 0.69-0.84, $p < 0.0001$) and hospital length of stay (relative risk 0.68; 95% CI 0.66-0.71, $p < 0.0001$) but did not have a significant effect on patient mortality.

Conclusions: Use of an AKI-SCAMP clinical decision support tool for assessment and management of AKI-RRT led to reduced ICU and hospital length of stay, 30-day hospital readmission rates, and use of RRT in cases of physician perceived treatment futility. We

advocate for increased use of this clinical decision support tool that has been shown to improve outcomes for patients with AKI.

6.2 Introduction

Acute kidney injury (AKI) is common and harmful, with clinical outcomes contingent on optimal management. AKI complicates 20% of inpatient admissions and is seen at rates as high as 30-50% in the intensive care unit (ICU) (Gallagher., 2014). Patients with AKI treated with renal replacement therapy (RRT) in the ICU have increased mortality over a 10-year follow-up period. The attributed costs of AKI in the United States are estimated to be $10 billion dollars annually (Star., 1998). AKI is also associated with high resource utilisation, including a longer length of stay both in the ICU and in the hospital (Vandijck., 2007). Individuals who survive an AKI-related hospitalisation have a greater likelihood of a recurrent hospital admission, compared with those with no evidence of kidney disease and are at increased risk of developing end stage kidney disease (ESKD) (See., 2019; Sawhney., 2017).

Delays in initiating RRT for AKI can result in serious preventable complications and even death (Bagshaw., 2009). However, initiating RRT carries procedural risks, including infection and bleeding, for patients who may recover renal function without requiring RRT. Recent randomised controlled trials have not conclusively shown a survival benefit of early versus late initiation of RRT for AKI (Gaudry., 2016; Zarbock., 2016; Barbar., 2018; the STARRT-AKI Investigators., 2020). To address uncertainty and variation in the care of patients with AKI requiring RRT, we implemented a structured decision-making algorithm (Standardised Clinical Assessment and Management Plan or SCAMP) over a 13-month period for clinicians managing patients with AKI in the medical ICU (MICU) (Mendu., 2017). The AKI-SCAMP algorithm provided recommendations about optimal indications for initiating and discontinuing RRT on the basis of evidence-based clinical parameters. AKI-SCAMP guidelines for RRT initiation included metabolic acidosis with pH < 7.2, hyperkalemia with serum potassium > 6.5 mmol/L or with EKG changes, toxin ingestion, massive anasarca, hypoxaemic respiratory failure with FiO2 > 0.7, urine output < 100 ml/24 hours and uraemic signs or symptoms. In this prior hypothesis-generating study, we found that patients whose clinicians adhered to the AKI-SCAMP recommendation to start RRT had lower in-hospital

mortality and 60-day mortality, compared to those whose clinicians did not adhere to these recommendations. In particular, AKI-SCAMP recommendation adherence was associated with lower in-hospital mortality for patients with low disease severity, but no significant association was seen for patients with high disease severity.

In order to better understand the impact of the AKI-SCAMP on clinical outcomes such as 30-day, 60-day hospital mortality, hospital and ICU length of stay, and readmission, we implemented a block randomised design, which involved alternating the AKI-SCAMP with a "sham" SCAMP, which did not provide guidance on RRT initiation, but did include questions related to estimated risk of mortality and treatment futility. In this study we hoped to ascertain if there was utility in using the AKI-SCAMP regardless of adherence to the recommended algorithm, in a broad population of all ICU patients in our institution. We also introduced clinical decision-making related to tunnelled dialysis catheter (TDC) placement for AKI and the accuracy of physician estimation of mortality and futility.

6.3 Methods

6.3.1 Description of the Standardized Clinical Assessment and Management Plan

A SCAMP is a quality improvement approach that involves implementation of a standardised care pathway, to an area of care delivery with uncertainty and variation in practice, in order to optimise outcomes. The iterative development of the AKI-SCAMP was previously described in an observational study published in the Clinical Journal of the American Society of Nephrology in 2017 (Mendu., 2017). Through an unstructured, iterative process involving four intensive care unit (ICU) nephrology attending physicians, we identified several areas of uncertainty in the care of patients with severe AKI, including criteria for RRT initiation and discontinuation. Specific criteria were agreed on by nephrologists on the basis of clinical experience and review of existing literature.

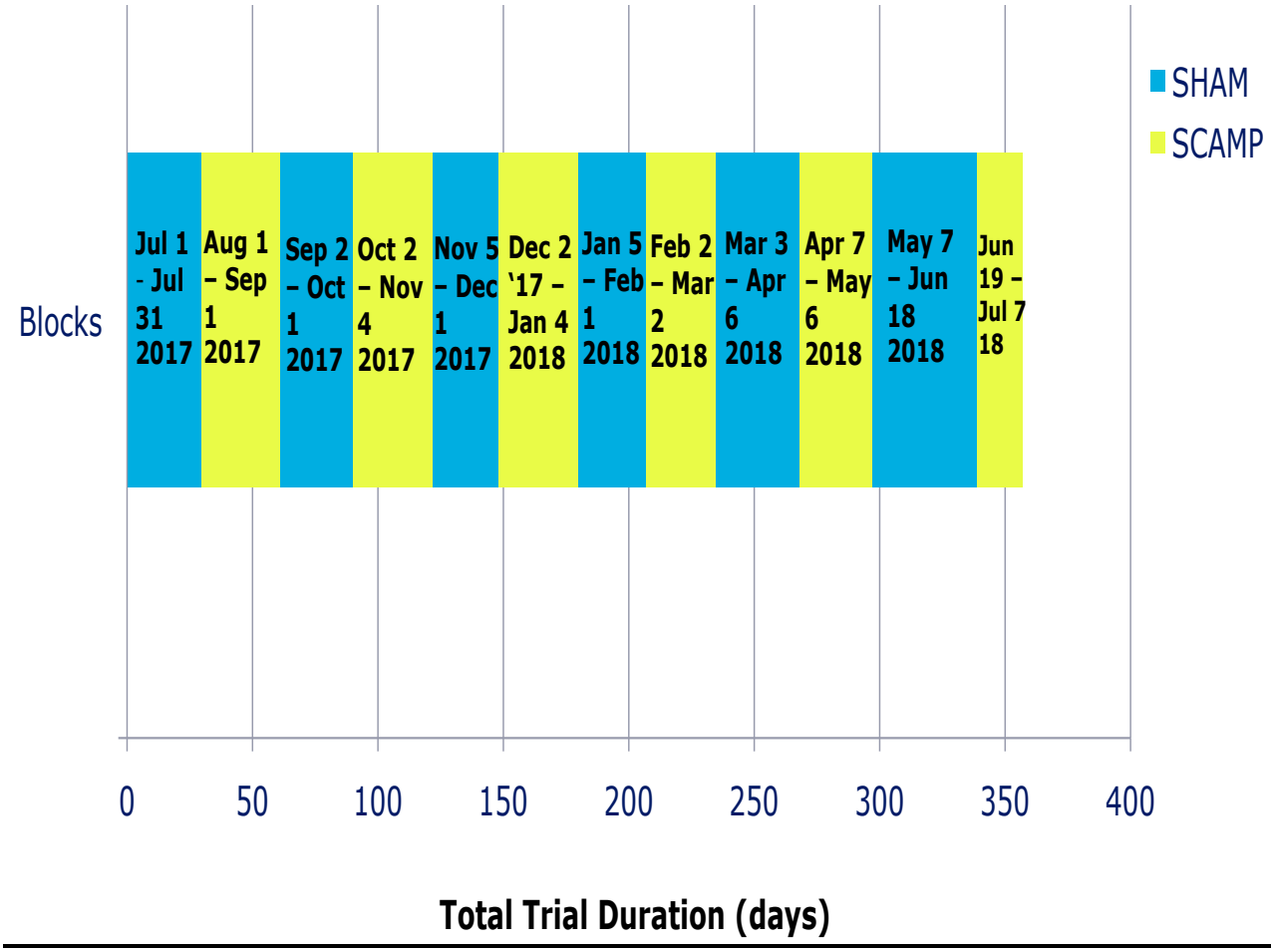
In practice, the AKI-SCAMP exists as an electronic or paper form provided to the nephrologist at the point-of-care. The nephrologist uses the form during the patient encounter to document relevant patient information and guide decision-making. The AKI-SCAMP algorithm provides indications for initiating RRT. It also includes questions related to

treatment futility (“If you are considering RRT, do you think RRT may extend life, but is unlikely to result in meaningful quality of life?”), which recommend that RRT should not be initiated under those circumstances. If the nephrologist decides to deviate from AKI-SCAMP recommendations, this diversion and the reasons for doing so are captured. Data collected from the form and the medical record are analysed and used to modify and iteratively improve the AKI-SCAMP algorithm; thereby, providing a continuous improvement program for learning.

6.3.2 Study Design

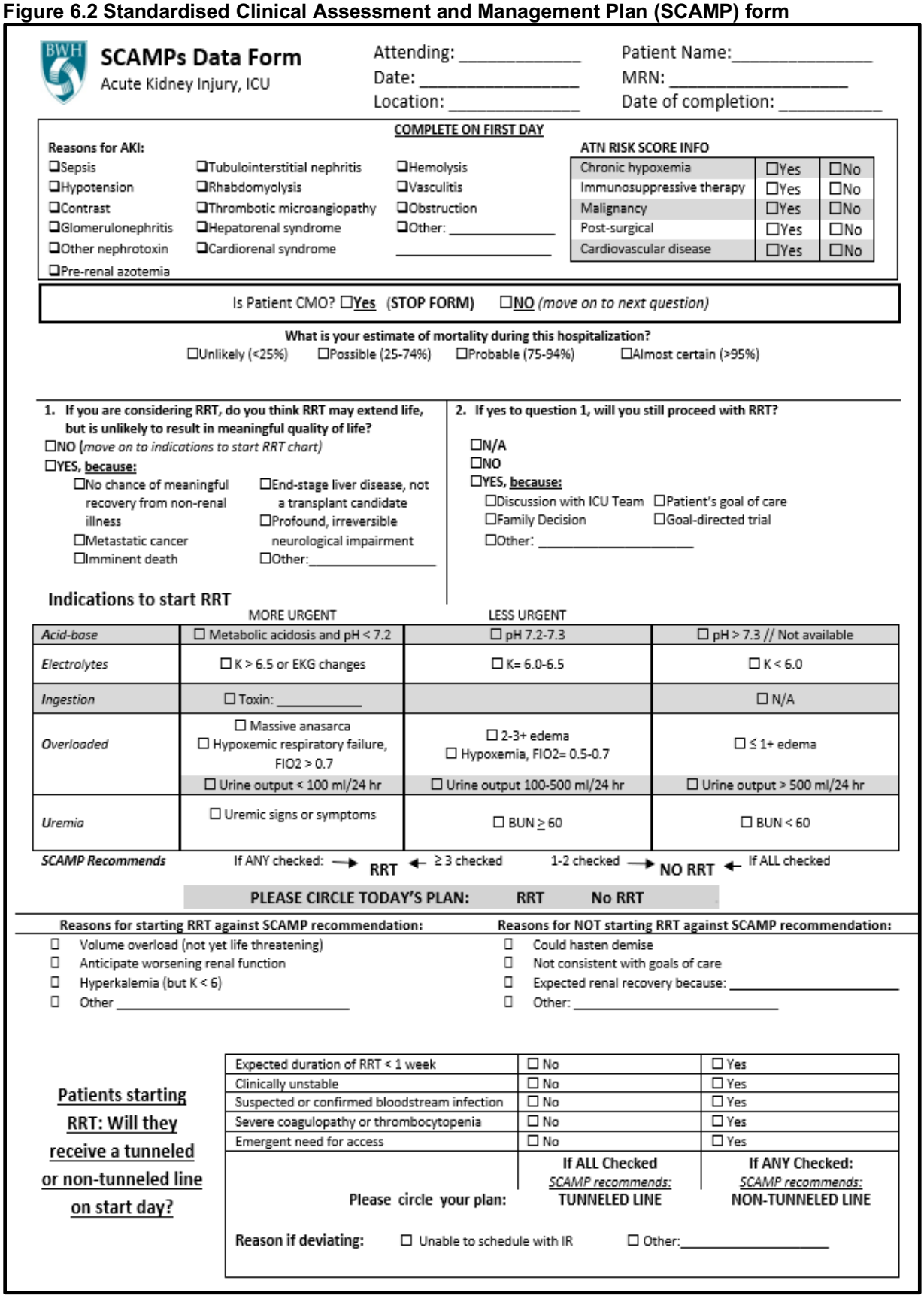
We conducted a block randomised clinical trial of AKI-SCAMP use between July 2017 and July 2018, in which critical care attending nephrologists completed AKI-SCAMP algorithm forms during a 4-6-week period, with a “sham” form used in alternating 4 to 6-week increments, as depicted in Figure 6.1. There was an additional adjudication step performed in which a data coordinator ensured that attendings had a balanced allocation of AKI-SCAMP versus sham periods (for example, ensuring one attending would not be assigned to only AKI-SCAMP or only sham). Figure 6.2 illustrates the AKI-SCAMP form that was used. The AKI-SCAMP form consists of questions related to patient comorbidities, reasons for AKI, physician-estimated mortality and futility, a decision-making algorithm for RRT initiation; and a decision-making algorithm for choice of tunnelled versus non-tunnelled dialysis catheter when RRT initiation was indicated. The sham form consisted of an abbreviated version of the AKI-SCAMP form, with reasons for AKI, estimated mortality and futility, without the RRT and TDC decision making algorithms, and is shown in Figure 6.3. We hypothesized that use of a sham form would address the possibility that the additional step of completing a form, as opposed to the specific AKI-SCAMP algorithm, could impact outcomes in a manner similar to the Hawthorne effect (McCambridge., 2014).

Figure 6.1 Schedule of Intervention (SCAMP) versus Control (SHAM) form block randomisation



Abbreviations: SCAMP: Standardised Clinical Assessment and Management Plan.
Sham: Control form.

Figure 6.2 Standardised Clinical Assessment and Management Plan (SCAMP) form



SCAMPs Data Form
Acute Kidney Injury, ICU

Attending: _____ Patient Name: _____
Date: _____ MRN: _____
Location: _____ Date of completion: _____

COMPLETE ON FIRST DAY

Reasons for AKI:

- ☐Sepsis
- ☐Hypotension
- ☐Contrast
- ☐Glomerulonephritis
- ☐Other nephrotoxin
- ☐Pre-renal azotemia
- ☐Tubulointerstitial nephritis
- ☐Rhabdomyolysis
- ☐Thrombotic microangiopathy
- ☐Hepatorenal syndrome
- ☐Cardiorenal syndrome
- ☐Hemolysis
- ☐Vasculitis
- ☐Obstruction
- ☐Other: _____

ATN RISK SCORE INFO

Chronic hypoxemia	☐Yes	☐No
Immunosuppressive therapy	☐Yes	☐No
Malignancy	☐Yes	☐No
Post-surgical	☐Yes	☐No
Cardiovascular disease	☐Yes	☐No

Is Patient CMO? ☐Yes (STOP FORM) ☐NO *(move on to next question)*

What is your estimate of mortality during this hospitalization?
☐Unlikely (<25%) ☐Possible (25-74%) ☐Probable (75-94%) ☐Almost certain (>95%)

1. If you are considering RRT, do you think RRT may extend life, but is unlikely to result in meaningful quality of life?
☐NO (*move on to indications to start RRT chart*)
☐YES, because:
- ☐No chance of meaningful recovery from non-renal illness
- ☐Metastatic cancer
- ☐Imminent death
- ☐End-stage liver disease, not a transplant candidate
- ☐Profound, irreversible neurological impairment
- ☐Other: _____

2. If yes to question 1, will you still proceed with RRT?
☐N/A
☐NO
☐YES, because:
- ☐Discussion with ICU Team
- ☐Patient's goal of care
- ☐Family Decision
- ☐Goal-directed trial
- ☐Other: _____

Indications to start RRT

	MORE URGENT	LESS URGENT	
Acid-base	☐ Metabolic acidosis and pH < 7.2	☐ pH 7.2-7.3	☐ pH > 7.3 // Not available
Electrolytes	☐ K > 6.5 or EKG changes	☐ K= 6.0-6.5	☐ K < 6.0
Ingestion	☐ Toxin: _____		☐ N/A
Overloaded	☐ Massive anasarca ☐ Hypoxemic respiratory failure, FIO2 > 0.7	☐ 2-3+ edema ☐ Hypoxemia, FIO2= 0.5-0.7	☐ ≤ 1+ edema
	☐ Urine output < 100 ml/24 hr	☐ Urine output 100-500 ml/24 hr	☐ Urine output > 500 ml/24 hr
Uremia	☐ Uremic signs or symptoms	☐ BUN ≥ 60	☐ BUN < 60

SCAMP Recommends If ANY checked: → **RRT** ← ≥ 3 checked 1-2 checked → **NO RRT** ← If ALL checked

PLEASE CIRCLE TODAY'S PLAN: RRT No RRT

Reasons for starting RRT against SCAMP recommendation:
- ☐ Volume overload (not yet life threatening)
- ☐ Anticipate worsening renal function
- ☐ Hyperkalemia (but K < 6)
- ☐ Other _____

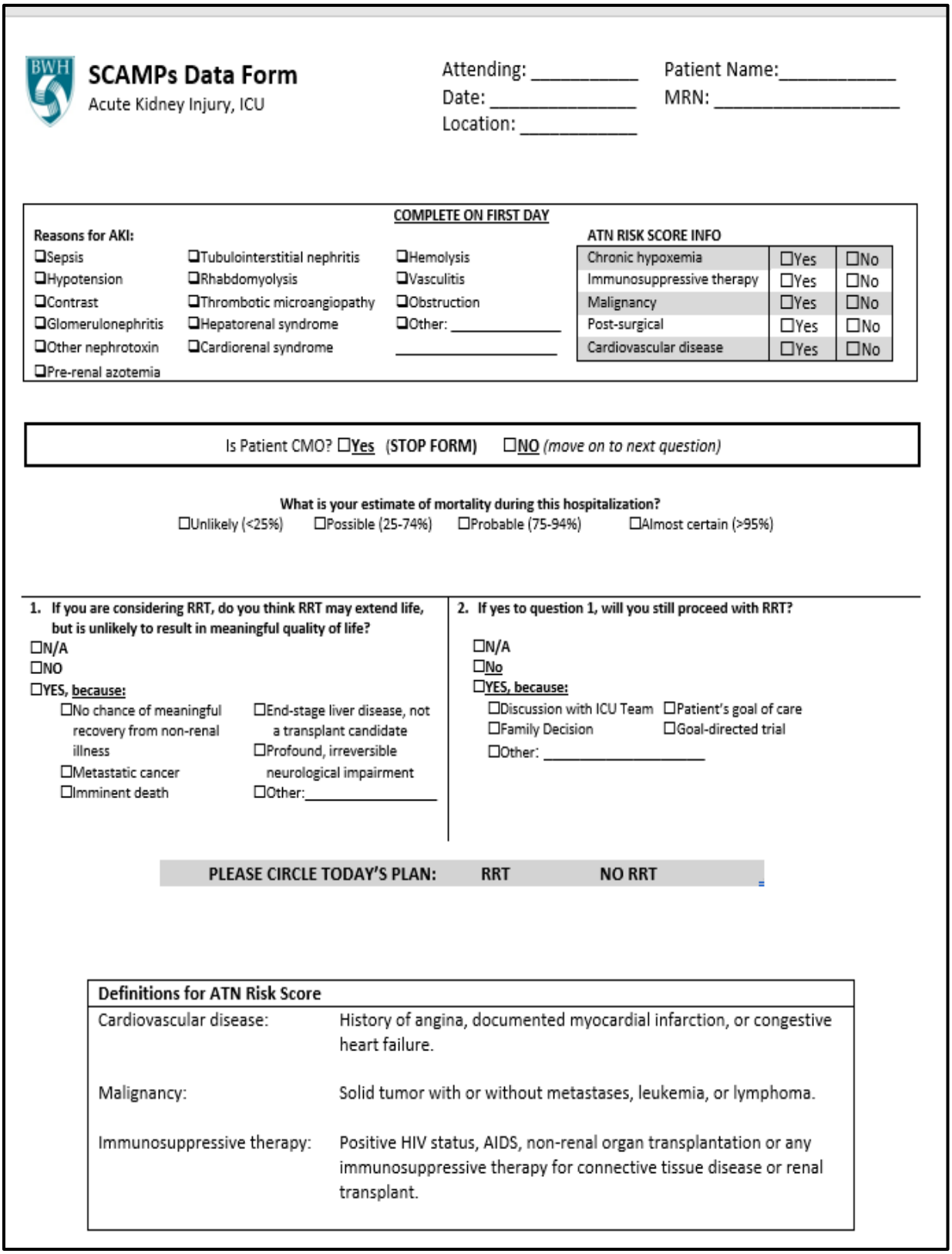
Reasons for NOT starting RRT against SCAMP recommendation:
- ☐ Could hasten demise
- ☐ Not consistent with goals of care
- ☐ Expected renal recovery because: _____
- ☐ Other: _____

Patients starting RRT: Will they receive a tunneled or non-tunneled line on start day?

Expected duration of RRT < 1 week	☐ No	☐ Yes
Clinically unstable	☐ No	☐ Yes
Suspected or confirmed bloodstream infection	☐ No	☐ Yes
Severe coagulopathy or thrombocytopenia	☐ No	☐ Yes
Emergent need for access	☐ No	☐ Yes
	If ALL Checked *SCAMP recommends:*	**If ANY Checked:** *SCAMP recommends:*
Please circle your plan:	**TUNNELED LINE**	**NON-TUNNELED LINE**

Reason if deviating: ☐ Unable to schedule with IR ☐ Other: _____

Figure 6.3 Control ("Sham") form



SCAMPs Data Form
Acute Kidney Injury, ICU

Attending: _____ Patient Name:_____
Date: _____ MRN: _____
Location: _____

COMPLETE ON FIRST DAY

Reasons for AKI:

- ❑Sepsis
- ❑Hypotension
- ❑Contrast
- ❑Glomerulonephritis
- ❑Other nephrotoxin
- ❑Pre-renal azotemia
- ❑Tubulointerstitial nephritis
- ❑Rhabdomyolysis
- ❑Thrombotic microangiopathy
- ❑Hepatorenal syndrome
- ❑Cardiorenal syndrome
- ❑Hemolysis
- ❑Vasculitis
- ❑Obstruction
- ❑Other: _____

ATN RISK SCORE INFO

Chronic hypoxemia	❑Yes	❑No
Immunosuppressive therapy	❑Yes	❑No
Malignancy	❑Yes	❑No
Post-surgical	❑Yes	❑No
Cardiovascular disease	❑Yes	❑No

Is Patient CMO? ❑Yes **(STOP FORM)** ❑NO *(move on to next question)*

What is your estimate of mortality during this hospitalization?
❑Unlikely (<25%) ❑Possible (25-74%) ❑Probable (75-94%) ❑Almost certain (>95%)

1. If you are considering RRT, do you think RRT may extend life, but is unlikely to result in meaningful quality of life?

❑N/A
❑NO
❑YES, because:

- ❑No chance of meaningful recovery from non-renal illness
- ❑Metastatic cancer
- ❑Imminent death
- ❑End-stage liver disease, not a transplant candidate
- ❑Profound, irreversible neurological impairment
- ❑Other:_____

2. If yes to question 1, will you still proceed with RRT?

❑N/A
❑No
❑YES, because:

- ❑Discussion with ICU Team
- ❑Family Decision
- ❑Other: _____
- ❑Patient's goal of care
- ❑Goal-directed trial

PLEASE CIRCLE TODAY'S PLAN: RRT NO RRT

Definitions for ATN Risk Score	
Cardiovascular disease:	History of angina, documented myocardial infarction, or congestive heart failure.
Malignancy:	Solid tumor with or without metastases, leukemia, or lymphoma.
Immunosuppressive therapy:	Positive HIV status, AIDS, non-renal organ transplantation or any immunosuppressive therapy for connective tissue disease or renal transplant.

6.3.3 Setting and Patient Population

This was a block randomised controlled trial of AKI-SCAMP algorithm use in all intensive care units at Brigham and Women's Hospital, a tertiary care academic medical center in Boston, Massachusetts. There are 9 ICUs in total – 2 medical, 2 surgical, 2 neurologic, 1 cardiac medical, 1, cardiac surgical, and 1 thoracic ICU, encompassing 90 beds. Approval was granted by the Institutional Review Board for data collection and analysis; the need for informed consent was waived as the research represented no more than a minimal risk of harm to subjects and involved no procedures for which written consent is normally required outside of the research context. A study coordinator identified eligible patients in the ICU, documented to have AKI by the nephrology ICU service. Patients with previous ICU admissions during hospitalisation were excluded. Patients were enrolled on the date that the initial nephrology service consultation was completed. Additional details regarding study design are provided in the supplemental material.

6.3.4 Attending Nephrologists

There were 8 critical care nephrologists who participated in the AKI-SCAMP trial at Brigham and Women's Hospital over the 12-month study period. 7/8 (87.5%) were male; with a median of 16 years since graduation from medical school (range 9-20 years) and a median of 7.5 years of experience attending in critical care nephrology (range 2-12 years).

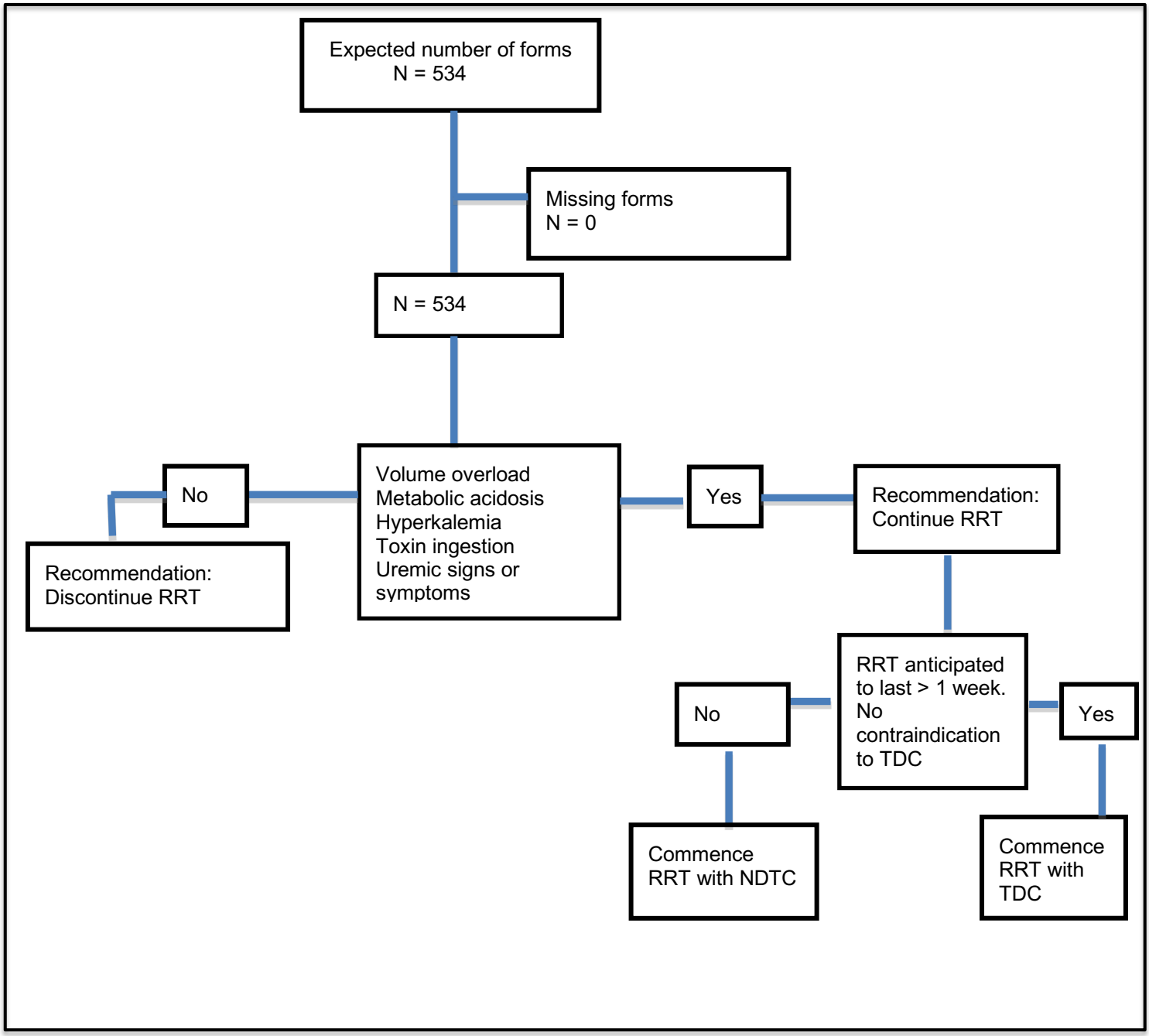
6.3.5 Study Implementation

Critical care nephrology attendings completed one data form per patient on each day of enrolment. Adherence to the AKI-SCAMP recommendations at the patient level was defined as adhering to all AKI-SCAMP recommendations regarding RRT initiation every day that the patient was enrolled in the AKI-SCAMP. Patients were considered to have completed the AKI-SCAMP on death, discharge, transfer from ICU, or nephrology team signing off.

Figure 6.4 shows the AKI-SCAMP workflow for RRT initiation. For patients not on RRT, each day clinicians entered clinical data relevant to AKI initiation (pH, potassium, suspicion of toxic ingestion, volume overload, fraction of inspired oxygen, urine output, BUN, and uremic symptoms). On the basis of the presence or absence of pre-specified criteria, the

AKI-SCAMP recommended whether to initiate RRT. Clinicians were free to follow or ignore the recommendation but asked to provide reasons for deviation if recommendations were ignored. The AKI-SCAMP also gave recommendations as to whether a non-tunnelled dialysis catheter (NTDC) or TDC should be used for RRT. TDC placement was recommended if RRT was predicted to be required for ≥ 1 week if no contraindications to TDC placement present (clinical instability; bloodstream infection; coagulopathy and emergent need for access).

Figure 6.4 Standardized Clinical Assessment and Management Plan (SCAMP) trial workflow



6.3.6 Data Sources and Collection

The BWH electronic medical record (EPIC, Partners version) was used to abstract data from nephrology consult notes as well as demographics, comorbidities, and laboratory results. Data related to vital signs, urine output, fluid balance, and RRT were obtained from the patients' daily flow sheets. Data about clinician adherence or deviation, reasons for deviation, and causes of AKI were obtained from the SCAMP forms. Compliance with completion of the AKI-SCAMP forms was monitored by a data coordinator, who followed attending nephrologists daily to ensure form completion.

6.3.7 Statistical Analyses

Patient demographic and clinical characteristics are reported as counts and percentages or medians and interquartile ranges (IQRs) as appropriate; comparisons between intervention and control patient characteristics were made with the t-test, Wilcoxon-rank sum test, and Fisher's exact test for normal and non-normal distributed covariates, respectively. The primary outcome was the risk of inpatient mortality between the AKI-SCAMP and sham groups. Secondary outcomes of interest included 30-day mortality, 60-day mortality, hospital length of stay, ICU length of stay, dialysis dependence at hospital discharge and 30-day readmission rate to the hospital and ICU.

Categorical outcomes were assessed in the two arms using Fisher's exact test as well as univariable and multivariable logistic regression; multivariable models were used to estimate the impact of the SCAMP on categorical outcomes adjusting for age, albumin, race, sex, sepsis and AKI– specific disease severity at enrolment (co-variates were selected based on significant differences between intervention and control cohorts, as well as established potential confounders i.e. race). Disease severity was estimated using the mortality risk equation by Demirjian et al derived in an RCT of patients with AKI RRT (Demirjian., 2011). This risk score as been shown to have improved performance for mortality prediction in patients with AKI, compared with Sequential Organ Failure Assessment and Acute Physiology and Chronic Health Evaluation II scores.

ICU length of stay was measured from ICU admission (enrolment) until death or discharge from ICU. Hospital length of stay was measured from hospital admission until death

or discharge from the hospital. We used a Poisson regression model, both unadjusted and adjusted using the same covariates as above, to estimate the effect of use of the AKI-SCAMP on ICU and hospital length of stay. As a sensitivity analysis, we plotted Kaplan-Meier curves to display time from enrolment to ICU or hospital discharge, with censoring due to death, in patients randomised to receive the AKI-SCAMP vs sham control; curves were compared using the log-rank test. Within the intervention group, we measured adherence to the AKI-SCAMP recommendations and subsequently assessed mortality and length of stay according to AKI-SCAMP adherence subgroups.

The AKI-SCAMP form also included a decision-making algorithm for choice of NTDC versus TDC for those commencing RRT. We collected data on the number of line infections and blood cultures taken associated with use of the AKI-SCAMP versus sham form. We also assessed the risk of mortality and length of stay associated with AKI-SCAMP line adherence.

With both AKI-SCAMP and sham forms, we asked nephrology attendings to predict inpatient mortality for each patient in the following categories: 0-24%, 25-75%, 75-94% and ≥95%. We then compared physician-predicted inpatient mortality to ATN score 60-day mortality risk categories, and subsequently to actual 60-day mortality for each patient, using a non-parametric test to compare the areas under receiver-operator curves (C-statistics). We also asked the nephrology attendings to assess whether treatment futility was present for each patient being considered for RRT. Treatment futility was defined as no meaningful chance of recovery from non-renal illness; imminent death; untreatable metastatic cancer, end-stage liver disease for which the patient was not a transplant candidate and severe irreversible neurological injury.

6.3.8 Sample size calculation

Using SAS Statistical Software, we used the results from our 2017 AKI-SCAMP observational study to estimate that a sample size of 110 patients per study arm would give us 80% power, with a 2-sided Type 1 error of 0.05, to detect a minimum in hospital mortality difference of 40% versus 60% between the SCAMP and sham groups.

6.4 Results

6.4.1 Clinical Characteristics

122 patients were assigned to the AKI-SCAMP study arm and 102 patients were assigned to the sham control study arm (Figure 6.5). Table 6.1 shows the characteristics of the 224 patients included in the study. There was no difference in the mean age of the participants in the intervention and control groups. There were significantly more men in the intervention group compared to the control group (69.7% vs 56.9%; p = 0.05). Most patients were white in both the intervention and control arms (82.8% vs 78.4%) but there was no significant difference in racial distribution between the two groups. Hypotension (62.3% vs 62.8%) and sepsis (32% vs 44.1%, p-value of 0.07) were the most common cause for AKI in both intervention and control groups. There was no difference in the frequency of underlying health conditions, vital signs at enrolment, laboratory values at enrolment and types of RRT received between the two groups.

Figure 6.5: Consort Flow Diagram for the AKI-SCAMP Trial

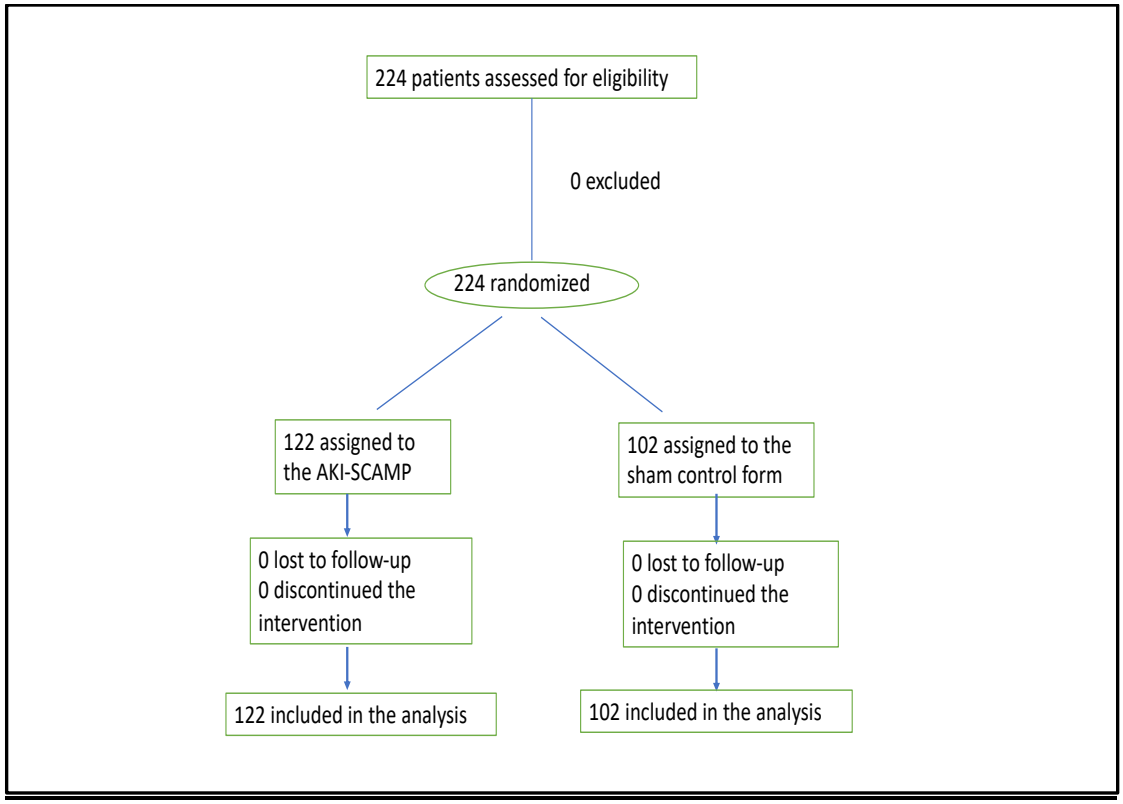


Table 6.1: Patient demographics and clinical characteristics

Patient characteristics	**Intervention N = 122**	**Control N = 102**	p-value
Male	85/122 (69.7%)	58/102 (56.9%)	0.05
Age, year, mean (SD)	62.2 (14.1)	63.4 (14.3)	0.41
Race N (%)			
White	101/122 (82.8%)	80/102 (78.4%)	0.39
Black	10/122 (8.2%)	15/102 (14.7%)	
Hispanic	8/122 (6.6%)	4/102 (3.9%)	
Other	3/122 (2.5%)	3/102 (2.9%)	
Intensive Care Unit location N (%)			
Medical	48/122 (39.3%)	42/102 (41.2%)	0.3
Cardiac medical	25/122 (20.5%)	19/102 (18.6%)	
Cardiac surgical	19/122 (15.6%)	13/102 (12.7%)	
Surgical	15/122 (12.3%)	15/102 (14.7%)	
Thoracic surgical	10/122 (8.2%)	3/102 (2.9%)	
Neurological	4/122 (3.3%)	8/102 (7.8%)	
Reasons for acute kidney injury N (%)			
Hypotension	76/122 (62.3%)	64/102 (62.8%)	1.00
Sepsis	39/122 (32%)	45/102 (44.1%)	0.07
Other	28/122 (23%)	13/102 (12.8%)	0.06
Contrast	21/122 (17.2%)	14/102 (13.7%)	0.58
Cardiorenal syndrome	16/122 (13.1%)	18/102 (17.7%)	0.36
Pre-renal azotemia	16/122 (13.1%)	7/102 (6.9%)	0.18
Other nephrotoxins	6/122 (4.9%)	8/102 (7.8%)	0.42
Hepatorenal syndrome	5/122 (4.1%)	1/102 (1.0%)	0.22
Obstruction	2/122 (1.6%)	1/102 (1%)	1.00
Rhabdomyolysis	1/122 (0.8%)	4/102 (3.9%)	0.18
Tubulointerstitial nephritis	1/122 (0.8%)	1/102 (1.0%)	1.00
Thrombotic microangiopathy	1/122 (0.8%)	1/102 (1.0%)	1.00
Glomerulonephritis	0/122 (0%)	1/102 (1.0%)	0.46
Hemolysis	0/122 (0%)	0/102 (0%)	1.00
Vasculitis	0/122 (0%)	0/102 (0%)	1.00
Chronic health conditions, N (%)			
Cardiovascular disease	60/122 (49.2%)	53/102 (52.0%)	0.69
Post-surgery	39/122 (32.0%)	30/102 (29.4%)	0.77
Malignancy	33/122 (27.1%)	25/102 (24.5%)	0.76
Immunosuppressive therapy	26/122 (21.3%)	25/102 (24.5%)	0.63
Chronic hypoxaemia	18/122 (14.8%)	15/102 (14.7%)	1.00
Vitals at enrolment, mean (SD)			
Heart rate, bpm	91.7 (21.7)	94.7 (20.9)	0.3
Mean arterial pressure, mm Hg	81.6 (18.7)	79.7 (14.9)	0.4
Urine output, ml	239 (626.2)	249.6 (545.7)	0.44
Laboratory values at enrolment, mean (SD)			
Arterial partial oxygen pressure, mm Hg	119.7 (62.5)	118.2 (62.1)	0.87
Arterial pH	7.35 (0.1)	7.36 (0.1)	0.99
INR	1.78 (1.6)	1.64 (0.7)	0.48
Serum albumin, g/dl	3.0 (0.8)	2.9 (0.7)	0.08
Serum alkaline phosphatase, IU/L	123.3 (95.5)	123 (94.3)	0.98
Serum bicarbonate, mmol/L	20.7 (5.6)	20.9 (6.1)	0.79
Serum bilirubin, mg/dl	1.69 (2.5)	2.07 (4.3)	0.43
Serum creatinine, mg/dl	2.8 (2.0)	2.7 (1.5)	0.32
Serum phosphate, mg/dl	5.2 (1.8)	5.3 (2.0)	0.68
Platelet count (x 10^9/L)	168.7 (99.0)	178.8 (112.8)	0.39
Ventilation requirements at enrolment, N (%)			

Mechanical ventilation with FiO2 < 0.6	57/122 (46.7%)	49/102 (48.0%)	0.89
Mechanical ventilation with FiO2 > 0.6	20/122 (16.4%)	10/102 (9.8%)	0.17
No mechanical ventilation; FiO2 > 0.6	5/122 (4.1%)	3/102 (2.9%)	0.73
Types of renal replacement therapy during enrolment, N (%)			
None	57/122 (46.7%)	43/102 (42.2%)	0.93
CVVH	34/122 (27.9%)	31/102 (30.4%)	
CVVH and HD	20/122 (16.4%)	18/102 (17.7%)	
HD	11/122 (9%)	10/102 (9.8%)	

Abbreviations: SD, standard deviation; INR, international normalized ratio; CVVH, continuous renal replacement therapy; HD, hemodialysis.

6.4.2 Mortality

There was no difference in the primary outcome of frequency of inpatient, 30-day or 60-day mortality between the two groups (Table 6.2). There was no significant difference in the unadjusted or adjusted (age, albumin, ATN score, race, sex and sepsis) odds of inpatient, 30-day or 60-day mortality between the two groups (Table 6.3).

Table 6.2: Impact of SCAMP on Patient Outcomes (Unadjusted)

Patient Outcome	Intervention N = 122	Control N = 102	p-value
Mortality, N (%)			
Inpatient mortality	50/122 (41.0%)	48/102 (47.1%)	0.42
30-day mortality	43/122 (35.3%)	43/102 (42.2%)	0.34
60-day mortality	48/122 (39.3%)	44/102 (43.1%)	0.59
Length of stay, mean (SD)			
ICU length of stay, hours	192.6 (199.9)	277.9 (308.8)	0.02
Hospital length of stay, days	23.8 (21.2)	30.4 (31.3)	0.07
Mortality risk prediction			
Probability of 60-day mortality by ATN risk equation, %, mean (SD)	30% (26.0)	31.1% (26.9)	0.76
ATN mortality risk score, median (IQR)	23 (18-28)	22 (17-27)	0.29
RRT requirement			
Dialysis dependence at hospital discharge	10/122 (8.2%)	11/102 (10.8%)	0.65
No. of RRT days per patient, mean (SD)	0.2 (0.4)	0.2 (0.4)	0.80
30-day readmission, N (%)			
Readmission to the hospital within 30 days	8/122 (6.6%)	15/102 (14.7%)	0.05
Readmission to the ICU within 30 days	3/122 (2.5%)	6/102 (5.9%)	0.31
Line infections, N (%)			
No. of patients with line infection	8/122 (6.6%)	11/102 (10.8%)	0.34
No. of blood cultures taken, mean (SD)	2.5 (5.1)	4.9 (7.0)	0.003
No. of patients with positive blood cultures	8/122 (6.6%)	11/102 (10.8%)	0.34

Abbreviations: SD, standard deviation; ICU, intensive care unit; ATN, Acute Renal Failure Trial Network; IQR, interquartile range.

Table 6.3: Effect of SCAMP on patient mortality

	Univariable OR (95% CI)	Univariable p-value	Multivariable OR (95% CI)	Multivariable p-value
Inpatient mortality	0.78 (0.46-1.33)	0.36	0.71 (0.38-1.32)	0.27
30-day mortality	0.75 (0.44-1.29)	0.29	0.75 (0.4-1.39)	0.36
60-day mortality	0.86 (0.50-1.46)	0.57	0.78 (0.42-1.44)	0.43

6.4.3 Length of stay - ICU and Hospital

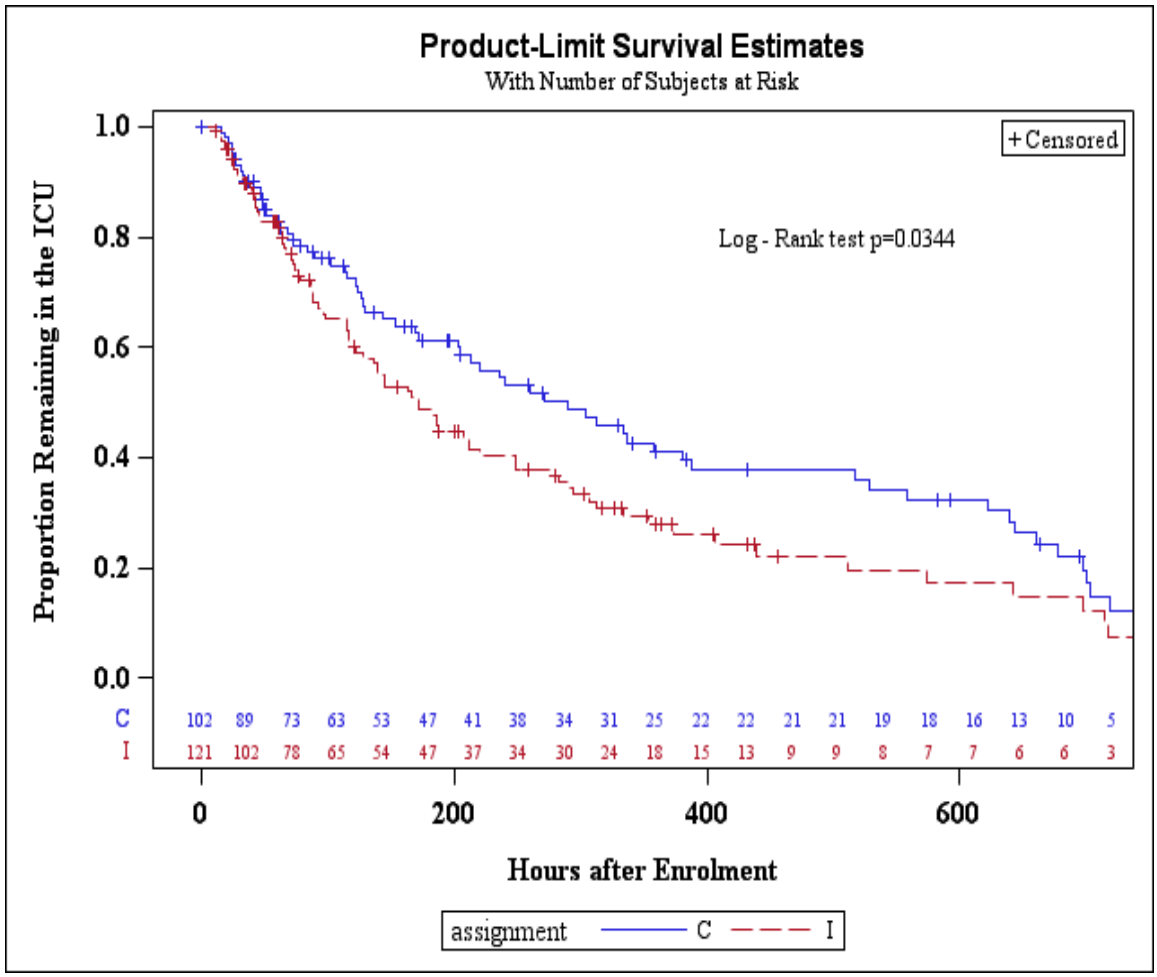
With respect to secondary outcomes, the mean ICU length of stay was shorter for patients in the intervention group compared to the control group (192.6 vs 277.9 hours; p = 0.02; Table 6.2). The median ICU length of stay in the intervention group was 117.6 hours (IQR 57.3-283.3 hours) compared to 163.3 hours (IQR 61.3-358.9 hours) for the control group. The unadjusted ICU length of stay was 31% shorter (29-32%) and the adjusted ICU length of stay was 33% shorter (31-34%) for patients in the intervention group compared to the control group (p < 0.0001 for both; Table 6.4). In a proportional hazards model censored for ICU mortality, ICU length of stay was significantly shorter for patients in the intervention group compared to the control group (log-rank test p = 0.03; Supplemental Figure 6.S1).

The mean hospital length of stay for the intervention group was 23.8 +/- 21.2 days compared to 30.4 +/- 31.3 days for the control group (p = 0.07). The median hospital length of stay in the intervention group was 17 days (IQR 10-35 days) compared to 21.5 days (IQR 11-38 days). The unadjusted hospital length of stay was 22% shorter (17-25%) and the adjusted hospital length of stay was 25% shorter (21-29%) for patients in the intervention group compared to the control group (p < 0.0001 for both; Table 6.4). In a proportional hazards model censored for inpatient mortality, hospital length of stay was still significantly shorter for patients in the intervention group compared to the control group (log-rank test p = 0.02; Supplemental Figure 6.S2). As a further sensitivity analysis, we adjusted both the proportional hazards model for ICU length of stay and the proportional hazards model for hospital length of stay for time period as a covariate to ensure that there was not a significant difference in either of these outcomes according to trends over time; given that the Kaplan-Meier curves appeared to diverge to a greater extent towards the latter part of the the study period. We found that both the adjusted ICU and hospital length of stay remained significantly shorter for patients in the intervention group despite adjusting for possible time trends as part of the final multivariable model.

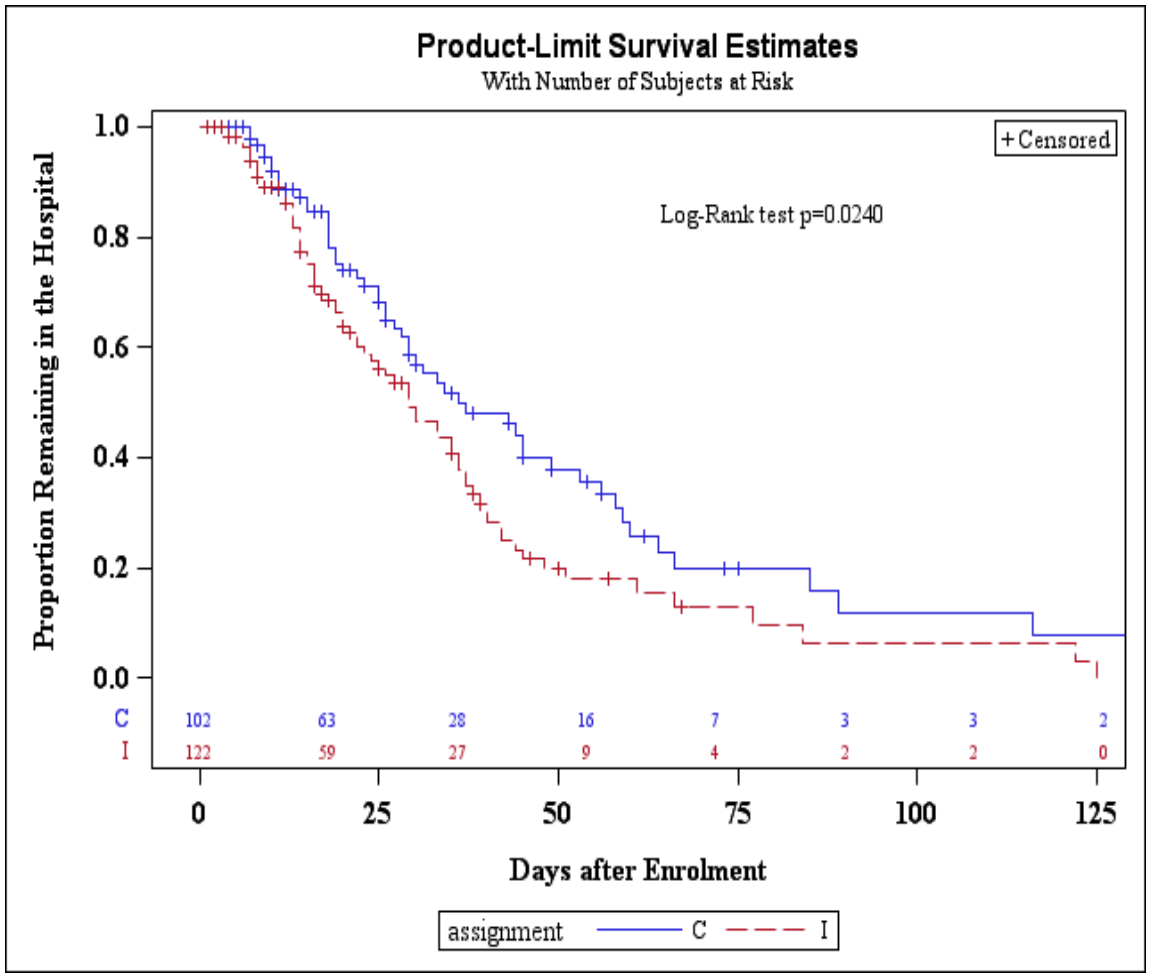
Table 6.4: Effect of SCAMP on length of stay

	Univariable RR (95% CI)	Univariable p-value	Multivariable RR (95% CI)	Multivariable p-value
Hospital length of stay	0.78 (0.75-0.83)	<0.0001	0.75 (0.72-0.79)	<0.0001
Intensive care unit length of stay	0.69 (0.68-0.71)	<0.0001	0.68 (0.66-0.69)	<0.0001

Supplemental Figure 6.S1: Kaplan-Meier curves for ICU length of stay according to treatment group; censoring for ICU mortality



Supplemental Figure 6.S2: Kaplan-Meier for hospital length of stay according to treatment group; censoring for inpatient mortality



6.4.4 Readmission

Fewer patients in the intervention group required hospital readmission within 30 days compared to those in the control group (6.6% vs 14.7%; p = 0.05; Table 6.2). The unadjusted odds of 30-day hospital readmission were significantly lower for patients in the intervention group compared to the control group (odds ratio 0.41; 95% CI 0.17-1.00; Table 6.5), while the adjusted odds of 30-day hospital readmission were significantly lower for patients in the intervention group compared to the control group (odds ratio 0.38; 95% CI 0.15-0.99). There was no significant difference in the unadjusted or adjusted odds of 30-day ICU readmission.

Table 6.5: Effect of SCAMP on 30-day readmission

	Univariable OR (95% CI)	Univariable p-value	Multivariable OR (95% CI)	Multivariable p-value
30-day hospital readmission	0.41 (0.17-1.00)	0.05	0.38 (0.15-0.99)	0.05
30-day intensive care unit readmission	0.4 (0.101.66)	0.21	0.41 (0.1-1.74)	0.22

6.4.5 Catheter-related infections

Fewer patients in the intervention group had either a NTDC (49.2% vs 52.9%) or a TDC (10.7% vs 19.6%) placed compared to the control group. The unadjusted number of blood cultures sent were 50% lower (42-57%) for the intervention group compared to the control group ($p < 0.0001$; Table 6.6). The adjusted number of blood cultures sent were 55% lower (47-61%) for the intervention group compared to the control group ($p < 0.0001$). There was no significant difference in either the unadjusted or adjusted odds of catheter-related infection between the two groups.

Table 6.6: Effect of SCAMP on catheter-related infections

	Univariable OR (95% CI)	Univariable p-value	Multivariable OR (95% CI)	Multivariable p-value
Catheter-related infection	0.58 (0.22-1.5)	0.26	0.44 (0.16-1.21)	0.11
Number of blood cultures sent	0.5 (0.43-0.58)	<0.0001	0.45 (0.39-0.53)	<0.0001

6.4.6 Adherence

There was an 8.5% overall rate of non-adherence to AKI-SCAMP recommendations in the intervention group (23/272 forms or patient-days, for 21/122 patients). Providers proceeded with RRT against AKI-SCAMP recommendations in 4.8% cases (13/272) (supplemental Table 6.S1). Reasons for deviation included hypervolemia (30.8% or 4/13 deviations), anticipated worsening of renal function (23.1% or 3/13 deviations), hyperkalemia (15.4% or 2/13 deviations) and other (30.8% or 4/13 deviations). Providers did not proceed with RRT against AKI-SCAMP recommendations in 6.6% cases (18/272) (supplemental Table

S1). Reasons for deviation included hastening demise (11.1% or 2/18 deviations), change in goals of care (44.4% or 8/18 deviations), expected renal recovery (38.9% or 7/18 deviations) and other (5.6% or 1/18 deviations).

In adjusted analyses at patient level in the AKI-SCAMP arm (Tables 6.7 and 6.8), there were no significant differences in inpatient mortality, 30-day mortality or 60-day mortality based on adherence to AKI-SCAMP form recommendations. Hospital length of stay was 24% shorter (16-31%) for patients with AKI-SCAMP adherence, and ICU length of stay was 32% (29-34%) longer for patients with AKI-SCAMP adherence compared to those patients whose providers were non-adherent to AKI-SCAMP recommendations.

Supplemental Table 6.S1: Reasons for deviation from AKI-SCAMP recommendations

Reasons for proceeding with RRT against AKI-SCAMP recommendations	**Percentage of total deviations N = 13**
Hypervolemia	4/13 (30.8%)
Anticipated worsening of renal function	3/13 (23.1%)
Hyperkalemia	2/13 (15.4%)
Other	4/13 (30.8%)
Reasons for not proceeding with RRT against AKI-SCAMP recommendations	**Percentage of total deviations N = 18**
Concern for hastening demise	2/18 (11.1%)
Change in goals of care	8/18 (44.4%)
Expected renal recovery	7/18 (38.9%)
Other	1/18 (5.6%)

Table 6.7: SCAMP adherence and patient outcomes (patient-level analysis) among patients in the SCAMP arm

Patient outcome	**SCAMP adherence**	**SCAMP non-adherence**	p-value
Inpatient mortality	43/101 (42.6%)	7/21 (33.3%)	0.43
30-day mortality	38/101 (37.6%)	5/21 (23.8%)	0.22
60-day mortality	43/101 (42.6%)	5/21 (23.8%)	0.10
Hospital length of stay, days, median (IQR)	17 (1-125)	22 (2-57)	0.001s
ICU length of stay, hours, median (IQR)	116.1 (11.1-1042)	173.9 (16.1-767.7)	<0.0001

Abbreviations: SD, standard deviation; IQR, interquartile range.

Table 6.8: Effect of SCAMP adherence on patient outcomes

	Univariable OR (95% CI)	Univariable p-value	Multivariable OR (95% CI)	Multivariable p-value
Inpatient mortality	1.48 (0.55-4.0)	0.44	1.54 (0.43-5.5)	0.5
30-day mortality	1.93 (0.65-5.7)	0.23	2.93 (0.78-11.1)	0.11
60-day mortality	2.37 (0.81-7.0)	0.12	3.33 (0.83-13.3)	0.09
Hospital length of stay	0.86 (0.78-0.94)	0.0008	0.76 (0.69-0.84)	< 0.0001
ICU length of stay	0.85 (0.82-0.88)	< 0.0001	0.68 (0.66-0.71)	< 0.0001

6.4.7 Treatment Futility

Significantly fewer RRT treatments were performed when physicians deemed the treatment to be futile in the intervention group compared to the control group (1.8% vs 7.3%, p=0.003, Table 6.9). There was no difference in the number of treatments performed due to family or primary team preference between the two groups (0.74% vs 1.9%). There was no difference in the median ATN score 60-day risk of mortality for patients for whom treatment was deemed to be futile. There was a trend towards significantly lower mortality in the intervention group of patients for whom treatment was deemed to be futile, compared to the control group (35.7% vs 73.3%, p = 0.07).

Table 6.9: SCAMP impact on renal replacement therapy decision-making when futility indicated

Patient outcome	**Intervention N (%)**	**Control N (%)**	**p-value**
RRT proceeded when physician felt that treatment was futile	5/272 (1.8%)	19/262 (7.3%)	0.003
RRT proceeded against physician wishes due to primary team/family preference	2/272 (0.74%)	5/262 (1.9%)	0.28
ATN score 60-day risk of mortality for treatment futility subgroup, median + IQR	38 (24-65)	36 (22-75)	C-statistic 0.72 (p-value 0.44)
Actual 60-day mortality for treatment futility subgroup	5/14 (35.7%)	11/15 (73.3%)	0.07

6.4.8 Mortality Risk Prediction

Physician-predicted mortality risk and ATN-predicted mortality risk were divided into 4 categories (<25%, 25-74%, 75-94% and ≥95%). Using Spearman correlation, physician-predicted mortality was weakly correlated with the ATN score (r = 0.3; p = 0.003) in the control group. There was no significant correlation between physician-predicted mortality and the ATN score in the intervention group. ATN score performed better with respect to prediction of 60-day mortality; with an area under the curve of 0.73 (95% CI 0.66-0.79), compared to physician-predicted mortality with an area under the curve of 0.56 (95% CI 0.49-0.64; Figure 6.6).

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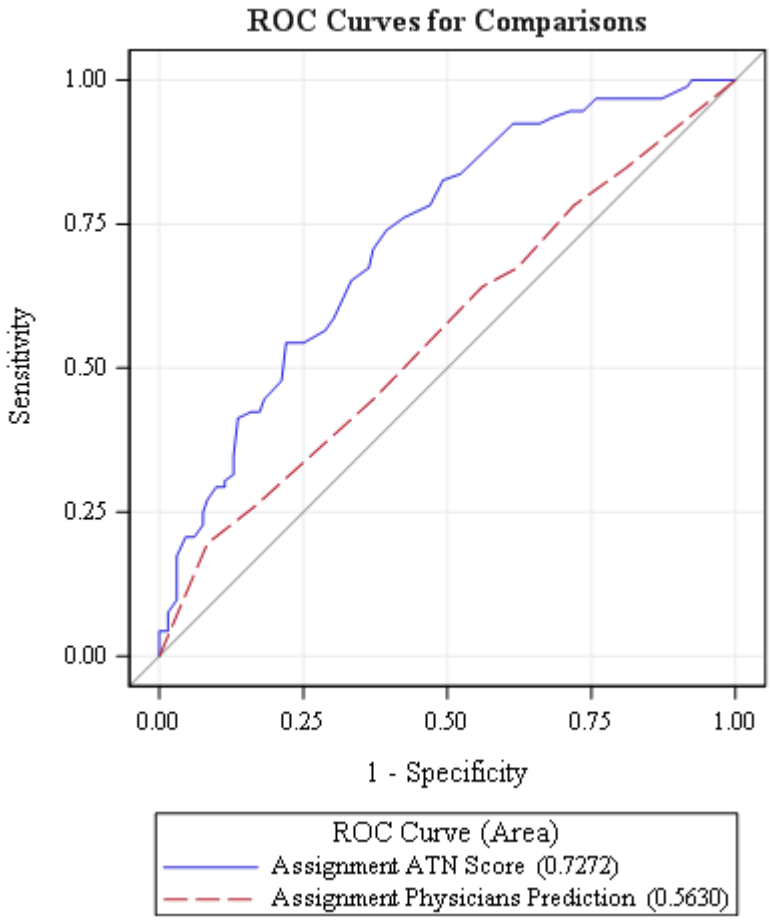
Figure 6.6: Receiver-Operator Curves for ATN integer score and physician-predicted mortality



ROC statistics

ROC model	Area under the curve	95% Lower confidence interval	95% Upper confidence interval	p-value
ATN score	0.73	0.66	0.79	0.001
Physician-predicted mortality	0.56	0.49	0.64	

Abbreviations: ATN, Acute Renal Failure Trial Network

6.5 Discussion

In this block randomised controlled trial, involving patients in multiple medical and surgical ICUs in a single tertiary academic US centre, we found that use of a clinical decision support system in the form of a SCAMP did not impact the primary outcome of in-hospital, 30-day or 60-day mortality, but did result in a significantly reduced ICU and hospital length of stay for patients with AKI, as well as a reduced 30-day hospital readmission rate. We also found that patients in the AKI-SCAMP intervention group were less likely to receive RRT despite physician-perceived treatment futility than those in the control group. The ATN integer score was found to be a significantly better risk predictor for inpatient and 60-day mortality in comparison to physician-predicted mortality.

There are few interventions that have been shown to improve outcomes for patients with AKI. The increased mortality and length of stay associated with AKI remains staggeringly high – with a 6.5 fold increase in mortality and a 3.5 fold increase in hospital length of stay reported by Chertow et al in recent years (Chertow., 2005). Challiner et al similarly found that the median length of stay for patients with AKI was 10 days compared to 4 days for patients without AKI in a large tertiary UK center (Challiner., 2014). However, some interventions in recent years have shown promise. Kolhe et al implemented a prospective observational study in which electronic recognition of AKI, coupled with an interruptive alert, was linked to an AKI care bundle, which included advice regarding AKI management (Kohle., 2015). Patients who had early completion of the AKI care bundle had lower odds of death at discharge, 30 days, 60 days and after a median of 134 days; however, the care bundle was only completed early in 2.2% of AKI cases. Similarly, the ICE-AKI prospective controlled interrupted time-series

study used an electronic clinical prediction rule which triggered an electronic AKI alert leading to a multidisciplinary team including physicians, nurses, pharmacists and critical care outreach reviewing the patient. They found that this reduced inpatient mortality for 2040 patients with hospital-acquired AKI (Hodgson., 2018). The PrevAKI randomized controlled trial found that implementing a care bundle based on the KDIGO guidelines (including optimization of volume status and haemodynamics, avoiding nephrotoxic drugs and preventing hyperglycemia) in 276 post-cardiac surgery patients deemed to be at high risk of AKI by urinary biomarker level (TIMP2:IGFBP7 > 0.3), significantly reduced the incidence of AKI, but did not however affect AKI severity, need for dialysis, length of stay and major adverse kidney events at day 30, 60 or 90 (Meersch., 2017). Selby et al performed a multicentre pragmatic clustered randomised trial which investigated use of a multifaceted intervention in 20,179 patients with AKI, including an AKI e-alert, an AKI care bundle including basic investigations and advice regarding assessment and management of AKI, and an education program for healthcare providers across the hospital sites (Selby., 2019). There was no significant improvement in 30-day mortality for those in the intervention group, but reduced hospital length of stay and improved AKI recognition, medication optimisation and fluid assessment, were seen. In summary, studies to date have focused on recognition of AKI and basic measures to prevent AKI progression in inpatient medicine populations. Our study has focused on a critically ill population in multiple ICU settings with severe AKI frequently requiring RRT, providing an algorithm for initiation of RRT and appropriate choice of vascular access when required.

Clinical guidelines related to AKI-RRT timing can have significant limitations. The trial populations from which they are derived may not reflect the real-life populations, due to specific inclusion and exclusion criteria which limit generalisability. They may also be subject to external influence that can lessen their validity (Coyne., 2002; Norris., 2011). One meta-analysis found that systematic reviews of RCTs, which form the basis of most clinical guidelines, have a “median survival time” of 5.5 years before they need an update (Shojania., 2007). Therefore, they do not always reflect the rapid changes which can occur in the acquisition of medical knowledge.

In contrast, standardized clinical assessment and management plans (SCAMPs) offer a clinician-designed approach to promoting care standardization that accommodates patients' individual differences, respects providers' clinical acumen and keeps pace with the rapid growth of medical knowledge. Various studies have acknowledged the impact of SCAMPs on increasing clinicians' rate of compliance with best evidence-based practices and on reducing medical costs for chronic disease by reducing the unnecessary use of resources (Farias., 2012; Verghese., 2012). SCAMPs have been shown to improve patient outcomes, such as in a study of catheterisation management for aortic stenosis in children, in which the rate of optimal results with balloon dilation significantly improved post introduction of a SCAMP (Porras., 2014). In addition, SCAMPs are associated with increased provider satisfaction ratings (Farias., 2011).

In this AKI-SCAMP block randomised controlled trial, there was no significant effect of the AKI-SCAMP clinical decision support tool on risk of mortality compared to controls. This is in contrast to our 2017 AKI-SCAMP observational study, which found a significant reduction in patient mortality associated with adherence to the AKI-SCAMP clinical decision support tool. However, in the original manuscript we had a more limited population, focused on the MICU of Brigham and Women's Hospital, and did not encompass the mixed medical, surgical, cardiothoracic and neurological populations which were included in our randomised controlled trial. There was a much higher rate of AKI-SCAMP non-adherence at 57% in our observational study, compared to an AKI-SCAMP non-adherence rate of just 8.5% in this clinical trial. This likely led to fewer delays in initiating RRT when needed, which may have reduced the impact of the AKI-SCAMP on mortality. Though use of alternating block randomised time period use of a sham form may have reduced the potential for a Hawthorne effect associated with improved outcomes through modification of physician decision-making by virtue of being observed with any type of form, we could also postulate that there may have been block-to-block carryover effects between the SCAMP and sham periods giving rising to learned behaviours that may have additionally biased our primary outcome towards the null. Our trial primary end-point was also essentially under-powered as the mortality rate in our control group was lower than that observed in our previous AKI-SCAMP observational study, therefore our power calculation for this trial under-estimated the patient numbers that

would be required to see a significant difference between the intervention and control groups. Our observational study also did not have a control group for comparison, and it utilised both nephrology fellows and attendings, as opposed to focusing specifically on critical care nephrology attendings.

Our AKI-SCAMP randomized trial did show a significant reduction in ICU and hospital length of stay; as well as in 30-day hospital readmission rates; acknowledging however that these were all secondary outcomes of the trial. Use of the AKI-SCAMP may have led to more judicious overall use of RRT and increased consideration of timely cessation of RRT when appropriate. Reduced use of RRT as a resource may have accounted for shortened hospital and ICU length of stay, and potentially reduced readmission rates due to reduced risk of complications associated with shortened exposure to this treatment modality and its associated procedural risks. Fewer patients in the AKI-SCAMP intervention arm also received RRT in the setting of physician-perceived treatment futility, which shows potentially more judicious use of RRT associated with the AKI-SCAMP intervention. These are all interesting and hypothesis-generating secondary end-points which merit further testing in future multi-centre randomised controlled trials.

We also evaluated physician mortality prediction in the AKI-SCAMP trial and found that the ATN integer score performed better than “best guess” physician-predicted mortality in predicting both inpatient and 60-day mortality. The ATN integer score was first derived by Demirjian et al using data from the Veteran Affairs/National Institutes of Health Acute Renal Failure Trial Network study to identify 21 independent predictors of 60-day mortality which outperformed existing generic and disease-specific scoring systems when applied in a logistic regression model (Demirjian., 2011; VA/NIH Acute Renal Failure Trial Network., 2008). These findings have subsequently been replicated in other large retrospective and prospective cohort studies (Bolanos., 2015; Carvalho., 2018). The accuracy of physician predicted risk of mortality in AKI has varied significantly in different studies. Allegretti et al. studied physician, nurse and patient/healthcare proxy perceptions of AKI-RRT prognosis and found that only 44% of physicians identified rates of survival that were consistent with the published literature (Allegretti., 2015). In a study of end-stage renal disease patients, Wachterman et al. found that chronic haemodialysis patients were significantly more optimistic in their estimates of 1-

year survival than their nephrologists (Wachterman., 2013). One approach that has been advocated for is training physicians to consider critical prognostic information in clinical decision-making by combining quantitative risk prediction tools with qualitative judgement, to facilitate better patient outcomes (Gill., 2012).

Strengths of our study are that the AKI-SCAMP was designed iteratively based on published data and expert consensus. We examined outcomes that are clinically relevant and inform practice. In addition, this was a block randomised controlled trial that was well-powered and included a large mixed medical, surgical, cardiac, cardiac surgical, thoracic surgical, neurological and neurosurgical population of patients over a 12-month period. The block randomisation design helped to ensure balance in numbers and patient characteristics. Our adjudication step allowed for balance in allocating each critical care nephrology attending equal exposure to both the SCAMP and SHAM form.

Limitations to our study include the fact that this was a single centre randomised controlled trial, which took place in a large academic teaching tertiary centre, and therefore may reduce the generalisability of our results in other settings. Our study encountered some challenges in implementing practical changes in AKI care delivery. We required a study coordinator to ensure daily form completion and attending nephrologists needed reminders to ensure form completion in some cases. Forms were completed retrospectively in some cases. We were unable to integrate the forms within the electronic health record as originally intended.

A larger multi-centre randomised controlled trial, involving ICUs in multiple hospitals in diverse settings, would be ideal to validate the results of our study and to provide further generalisability. However, given the compelling results both from our AKI-SCAMP observational study and this randomised controlled trial, we feel that there is substantial evidence to support use of AKI-SCAMP as a clinical decision support tool to guide decision-making regarding RRT initiation, in order to improve patient outcomes and reduce costs associated with length of stay, readmission and unnecessary treatment in cases of futility.

6.6 Conclusions

In summary, use of an AKI-SCAMP clinical decision support tool for assessment and management of AKI-RRT did not have a significant impact on inpatient, 30-day or 60-day mortality but did lead to reductions in ICU and hospital length of stay, reduced 30-day hospital readmission rates, and reduced use of RRT in cases of physician-perceived treatment futility. We advocate for increased use of this clinical decision support tool that has been shown to improve outcomes for patients with AKI.

Registration: Trial registered with ClinicalTrials.gov at https://clinicaltrials.gov/ct2/show/NCT03368183

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CHAPTER 7

Development of Consensus Guidelines for Discontinuation of AKI-RRT

7.1 Abstract

There is wide variation in clinical practice regarding timing of discontinuation of renal replacement therapy (RRT) in patients with acute kidney injury (AKI). Prolonged, unnecessary RRT treatment can contribute to length of stay, overall hospital costs, and risk of complications associated with RRT. In addition, prolonged RRT can paradoxically lengthen the time for which the patient remains dialysis-dependent. Well-designed, randomised clinical trials have utilised varied discontinuation criteria specifically related to urine output and creatinine clearance, which impedes the comparison of outcomes from such studies. Other observational studies have attempted to assess the sensitivity and specificity of various criteria for discontinuation of RRT. Whether diuretics influence renal recovery has not been fully elucidated as well. In this article, we propose a starting framework for RRT discontinuation criteria to guide clinicians and clinical researchers. We emphasise the importance of frequent clinical assessment while considering discontinuation of RRT for AKI patients with a creatinine clearance >15 mL/min on a timed urine collection and/or a urine output >400 mL/24 h without diuretics, or >2000 mL/24 h with diuretics. We also discuss newer biomarkers, methods of GFR estimation, and imaging techniques that may play a greater role in the future. Clinical trials objectively comparing the success of RRT discontinuation criteria will be required to provide high-quality evidence for our proposed guidelines.

7.2 Introduction

The delivery of renal replacement therapy (RRT) for patients with acute kidney injury (AKI) is extremely variable and based primarily on empiricism and local institutional practice (Mehta., 2004; Uchino., 2005; Ricci., 2006). In particular, there is little consensus regarding timing for discontinuation. The current KDIGO guidelines (KDIGO AKI Work Group., 2012) state:

> Discontinue RRT when it is no longer required, either because intrinsic kidney function has recovered to the point that it is adequate to meet patient needs, or because RRT is no longer consistent with the goals of care. (Not graded)

and

> We suggest not using diuretics to enhance kidney function recovery, or to reduce the duration or frequency of RRT (2B)

The potential advantages of ceasing RRT as early as possible include reducing length of stay (Bagshaw., 2005), overall hospital costs (Hamel., 1997), and exposure to the complications and adverse effects associated with RRT (Korkeila., 2000; Morgera., 2002). Extending RRT beyond its minimum required time may delay renal recovery and paradoxically lengthen the time for which the patient remains dialysis-dependent (McCausland., 2016; Vijayan., 2018). Decisions on RRT discontinuation can, therefore, significantly impact clinical outcomes.

The uncertainty regarding RRT discontinuation is illustrated by recent randomised controlled trials (RCTs) that used varied urine output cut-off criteria for determining timing of RRT discontinuation (summarized in Table 7.1). In Gaudry et al, discontinuation of RRT was "considered" if the spontaneous urine output was >500 mL/ 24 h, and "was highly recommended" if the spontaneous urine output was >1000 mL/24 h or >2000/24 h in the absence or presence of diuretic therapy, respectively (Gaudry., 2016). Discontinuation was mandatory if renal function was recovering with adequate volume control. In Zarbock et al, renal recovery was defined by (a) a urine output >400 mL/24 h without and 2100 mL/24 h with diuretic treatment and (b) a measured creatinine clearance >20 mL/min (Zarbock., 2016).

Similarly, in the Acute Renal Failure Trial Network (ATN) study, investigators performed 6-hour timed urine collection for creatinine clearance when the urine output exceeded 30 mL/h or when serum creatinine (SCr) decreased while on continuous RRT (CRRT). RRT was discontinued when the measured creatinine clearance exceeded 20 mL/min and was left to the discretion of providers when in the range of 12-20 mL/min (The VA/NIH Acute Renal Failure Trial Network., 2008). The investigators subsequently found that many study sites reported that the cut-off creatinine clearance of 20 mL/min resulted in

patients continuing RRT longer than deemed necessary; hence, an updated protocol ultimately lowered the threshold creatinine clearance for discontinuation of RRT to 12 mL/min for the remainder of the trial.

7.3 Consensus Guidelines for Discontinuation of AKI-RRT

The multiplicity of RRT discontinuation criteria used in high-quality multicentre RCTs evinces the need for consensus. Discrepant threshold criteria make it difficult to evaluate and compare outcomes from these trials (Table 7.1), and highlight the need to consolidate discontinuation criteria.

The criteria for defining "successful" discontinuation are also not clearly established. A reasonable definition could be: (a) no need to restart RRT and (b) renal recovery as defined by stable or declining serum creatinine with urine output >400 mL/24 h. Studies to date examining the utility of various criteria on predicting the successful discontinuation of RRT (i.e. RRT does not need to be restarted and the patient experiences some degree of renal recovery) have focused on two types of criteria: (a) urine volume over time and (b) renal creatinine clearance (summarized in Table 7.2). Some have incorporated concomitant diuretic therapy in their criteria.

The BEST Kidney (Beginning and Ending Supportive Therapy for the Kidney) study was a multicentre, multinational prospective epidemiologic study examining the association of clinical factors and processes of care with AKI outcomes. It included 1006 patients receiving CRRT during the study period; 313 successfully had RRT discontinued, defined as independence from RRT for at least 7 days after discontinuation of treatment (Uchino., 2009). The area under the ROC curve to predict successful discontinuation of CRRT was 0.81 (0.77-0.84) for urine output and 0.64 (0.59-0.68) for serum creatinine. The highest sensitivity and specificity for predicting renal recovery was a urine output >436 mL/24 h for patients not on diuretics and >2330 mL/24 h for patients receiving diuretics; the latter had a positive predictive value of 88%.

Viallet et al compared 24-hour urinary urea and creatinine to creatinine clearance, urea clearance, creatinine generation rate, urea generation rate, 24 hour diuresis, Simplified

Acute Physiology Score (SAPS) II, and Sequential Organ Failure Assessment (SOFA) scores to assess which of these factors were most significant in predicting successful RRT weaning for AKI patients (Viallet., 2016). By multivariate analysis, a 24-hour urinary creatinine clearance of 15 mL/min was the most powerful parameter associated with RRT discontinuation success; it had a negative predictive value of 82% and a positive predictive value of 84%. Similarly, another small study found that a 24-hour creatinine clearance >15 mL/min was associated with successful termination of CRRT, defined as the absence of CRRT requirement for at least 2 weeks (Shealy., 2003).

The "furosemide stress test" involves administering a one-time dose of 1 mg/kg IV furosemide to loop diuretic-naïve patients (or a 1.5 mg/kg dose for patients who had received loop diuretics within the previous 7 days). Lack of response to the furosemide stress test (urine output <200 mL within 2 hours after giving the diuretic dose) predicted development of AKI stage 3 (including a threefold increase in creatinine, oliguria for 24 hours or anuria for 12 hours) according to the AKI Network classification in a small prospective cohort of critically ill patients (Chawla., 2013). A positive response within 24 hours of cessation of CRRT predicted eventual renal recovery. In one small trial, furosemide increased urine volume and sodium excretion but did not shorten AKI duration or increase renal recovery (van der Voort., 2009). Diuretics may serve a role in prognostication, but whether diuretics could facilitate successful RRT discontinuation as part of the deresuscitation phase of fluid management has not been adequately studied. Certainly, they make discontinuation of dialysis easier in volume-overloaded patients.

The assessment of renal recovery for patients with AKI who are being managed with intermittent haemodialysis can be challenging due to the fluctuation of dialysable solute levels. Small solutes like blood urea nitrogen (BUN) and SCr are not in steady state, complicating the use of 24-hour urine clearances. Therefore, native kidney function—as assessed by timed urinary clearances—can only be assessed during the interdialytic period on non-dialysis days. This problem is easier to address on CRRT, where steady-state levels are usually achieved by the time discontinuation discussions arise. Given time constraints and

technical difficulty associated with collecting urine over a 24-hour period, 12-hour and even 6-hour urine collections have been used instead to calculate creatinine clearance and have been shown to be useful surrogate markers for decision-making regarding weaning of RRT and overall renal recovery (the VA/NIH Acute Renal Failure Trial Network., 2008; Fröhlich., 2012). Because of tubular secretion of creatinine, creatinine clearance overestimates the true GFR. Both the Jelliffe equation for unstable kidney function (Jelliffe., 2002) and the kinetic eGFR (Pianta., 2015) which utilize creatinine kinetics rather than steady-state parameters, have been used in small populations of select patients in an attempt to achieve a more accurate contemporaneous creatinine clearance for critically ill patients, but have not gained widespread use yet. Averaging urea and creatinine clearances is a more widely used approach to the GFR overestimation issue.

The most important pre-existing risk factor for non-recovery from AKI is CKD (Cole., 2000). The prevalence of CKD among critically ill patients with AKI is approximately 30% and is likely to increase in the context of an aging population (Uchino., 2005; Tsai., 2014). Lower premorbid function is more predictive of non-recovery and dialysis dependence probably because it indicates poor renal reserve to respond to the acute stress of critical illness and AKI. Hsu et al tracked the post-discharge outcomes of 39 805 hospitalized patients with baseline eGFR < 45 mL/min/1.73 m2 (Hsu., 2009). Among those with AKI, the risk of ESRD within 30 days post-discharge was 42% for those with eGFR 30-44 mL/min/1.73 m2 and 63% for those with eGFR 15-29 mL/min/1.73 m2 pre-hospitalization. Decision-making related to RRT discontinuation should reflect the additional risk and monitoring needed for patients with pre-existing CKD.

The role for biomarkers other than creatinine to assess renal recovery in AKI remains under investigation. For example, a recent prospective observational study measured serum cystatin C, NGAL and creatinine in 110 patients who were undergoing a trial of discontinuation of CRRT (Kim., 2018). However, only serum cystatin C was a significant independent predictor for successful CRRT discontinuation in a multivariable logistic regression model. Such use of biomarkers therefore remains largely experimental at present

and cannot yet be used as a primary assessment for renal recovery.

There are ongoing efforts to develop non-invasive imaging methods to characterize the extent of ongoing AKI and the potential for renal recovery. MRI-chemical exchange saturation transfer (CEST) pH imaging can be used to evaluate renal ischaemia reperfusion injury. In mouse models, it distinguishes the evolution from moderate to severe AKI (Longo., 2017) with subsequent restoration of normal pH values serving as an indicator for renal recovery (Longo., 2013). Arterial spin labelling perfusion MRI also accurately assesses cortical and medullary malperfusion in the setting of AKI, but the relationship between arterial spin labelling measurements and renal recovery could not be quantified (Dong., 2013). Further studies in humans will be needed to fully assess the sensitivity and specificity of imaging to provide timely, non-invasive information regarding AKI progression and recovery.

At our institution, we have found that there is significant variability in clinical practice related to discontinuation of RRT. We conducted a prospective cohort study in the medical intensive care unit at Brigham and Women's Hospital in which we implemented an AKI Standardized Clinical Assessment and Management Plan, which acted as a decision-making algorithm to assist front-line clinicians caring for patients with AKI (Mendu., 2017). 177 patients were enrolled in the study over a 13-month period. Discontinuation of RRT was recommended based on a pre-specified urine output cut-off criterion of >500 mL/24 h. However, despite these recommendations, clinicians chose to discontinue RRT in only 33% of such cases. The most common reasons for not adhering to the guideline were volume overload (69%), worsening serum creatinine (25%), and uraemia (17%). These findings indicate that one designated criterion will not be sufficient in isolation to guide RRT discontinuation.

7.4 Conclusions

Given the sparse literature on this topic, it is clear that there are no consensus criteria regarding RRT discontinuation. We believe that it is vital to establish objective criteria to guide clinical decision-making and inform study design. The rate of urine volume, creatinine

clearance, and subjective clinical criteria are considerations in our proposed framework. Our suggested guidelines for clinical decision-making on RRT discontinuation are shown in Figure 7.1 - we hope they can serve as a starting framework based on the existing evidence for RRT discontinuation indications. A prospective clinical trial that compares disparate clinical criteria (specifically, urine output and creatinine clearance) is required to establish clear guidelines for RRT discontinuation. Establishment of "STOP" criteria is a necessary step in ensuring that RRT discontinuation decision-making is evidence based, and could potentially improve outcomes by limiting RRT duration, delayed renal recovery, and hospital length of stay.

Table 7.1: Cut-off Criteria used in Clinical trials

Study	**Urine output**	**Creatinine clearance**	**Serum creatinine**
Gaudry., 2016	- Consider if spontaneous urine output > 500 ml/25 hours - Recommend if spontaneous urine output > 1000 ml/24 hours - Recommend if urine output > 2000 ml/24 hours with diuresis	N/A	Mandatory if diuresis sufficient to provide spontaneous decrease in serum creatinine
Zarbock., 2016	- Recommend if spontaneous urine output > 400 ml/24 hours - Recommend if urine output > 2100 ml/24 hours with diuresis	- Recommend if CrCl > 20 ml/min	N/A
VA/NIH Acute Renal Failure Trial Network., 2008	Perform 6 hour urine creatinine collection when urine output > 30 ml/hour	- Recommend if CrCl > 20 ml/min - Physician discretion if CrCl 12-20 ml/min - Continue RRT if CrCl < 12 ml/min	Perform 6 hour urine creatinine collection when spontaneous decrease in serum creatinine occurs on CRRT
van der Voort., 2009	Median urine output 247 ml/hour (IQR 774 ml/hour) on furosemide infusion at 0.5 mg/kg/hour versus 117 ml/hour (IQR 158 ml/hour) without diuresis. However, furosemide did not lead to any difference in renal recovery (p = 0.46).	N/A	N/A

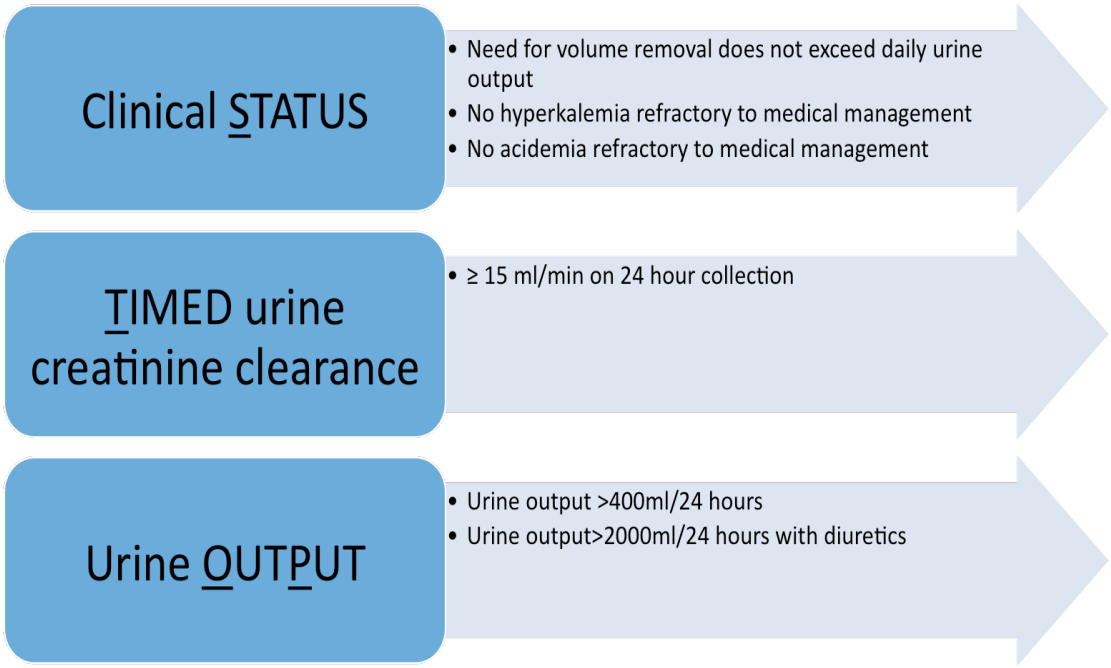
Abbreviations: CrCl, creatinine clearance; IQR, interquartile range; CRRT, continuous renal replacement therapy; N/A, not applicable.

Table 7.2: Predictive Criteria from Observational studies

Study	Urine output	AUC	Creatinine clearance	AUC
Uchino., 2009	- UO > 436 ml/24 hours without diuresis - UO > 2330 ml/24 hours with diuresis	0.85 (0.80-0.83) without diuretics; 0.67 (0.59-0.75) with diuretics	N/A	N/A
Viallet., 2016	> 2300 ml/24 hours with diuresis	0.66 (0.51-0.80)	24 hour urinary creatinine ≥ 5.2 mmol	0.86 (0.75-0.97)
Shealy., 2003	N/A	N/A	24 hour CrCl > 15 ml/min on day of CRRT discontinuation predictive of success for cohort of 10 patients	Not given
Chawla., 2013	2 hour urine output ≤ 200 ml predictive of progression to AKIN Stage III post furosemide bolus (1 mg/kg if diuretic naïve; 1.5 mg/kg if received diuretics within previous 7 days)	0.87 (0.82-0.92)	N/A	N/A

Abbreviations: UO, urine output; NA, not applicable; AUC, area under the curve; CrCl, creatinine clearance; AKIN, Acute Kidney Injury Network.

Figure 7.1: "STOP" criteria for consideration of RRT cessation



CHAPTER 8

Optimising Vascular Access Choice for AKI-RRT

8.1 Abstract

Renal replacement therapy (RRT) in the setting of acute kidney injury (AKI) is generally provided by either tunnelled or non-tunnelled dialysis catheters (TDCs or NTDCs), used immediately after insertion. Current consensus guidelines suggest using NTDCs rather than TDCs for vascular access in AKI primarily for logistical reasons, including ease of insertion and timeliness. However, there is increasing evidence that, compared to NTDCs, TDCs are associated with fewer complications (mechanical and infectious) and better dialysis delivery. Nevertheless, this evidence must be balanced by the feasibility and practicality of implementing a "TDC-first approach." In this paper, we assess the current evidence base for vascular access choice for AKI requiring RRT. We make the case for increased use of TDCs as first-line vascular access given growing observational evidence for improved patient outcomes; including decreased risk of infection and thrombosis, increased blood flow rates and decreased treatment interruptions, compared to NDTCs. We advocate for further research to test the feasibility and outcomes associated with a TDC-first approach to AKI-RRT access. A TDC-first approach has the potential to improve RRT clinical outcomes and reduce resource utilisation and cost.

8.2 Introduction

Acute kidney injury (AKI), defined by an abrupt decrease in kidney function resulting in the retention of waste products and in the dysregulation of extracellular volume and electrolytes, is common, associated with significant morbidity and mortality, and potentially treatable (KDIGO AKI Work Group., 2012). AKI complicates 20% of inpatient admissions and 30%-50% of intensive care unit (ICU) admissions (Star., 1998). Attributed costs of AKI in the United States are estimated at $10 billion annually (Vandijck., 2007). Despite decades of research, intermittent haemodialysis (IHD) or continuous renal replacement therapy (CRRT), remains the primary therapy to treat AKI and its complications. Initiation of renal replacement therapy (RRT) requires vascular access, in the form of intravenous catheters.

RRT in the setting of AKI is provided by either tunnelled or non-tunnelled dialysis

catheters (TDCs or NTDCs), used immediately after insertion. NTDCs are typically placed at bedside in the internal jugular or femoral vein by either nephrologists or intensivists; dynamic ultrasound guidance (as recommended by professional societies) reduces the risk of insertion-related complications (KDIGO AKI Work Group., 2012; Troianos., 2012., Pittiruti., 2009; Lamperti., 2012; Bodenham., 2016; Bouaziz., 2015., Rabindranath., 2011). TDCs are typically placed in the right internal jugular vein by interventional radiologists, interventional nephrologists, or vascular surgeons in procedural areas, with the aid of both ultrasound and fluoroscopic guidance.

Kidney Disease: Improving Global Outcomes (KDIGO) guidelines suggest using NTDCs rather than TDCs for vascular access in AKI (level of evidence, 2D), primarily for logistical reasons—namely, ease of insertion and timeliness (KDIGO AKI Work Group., 2012). However, the guidelines state that for patients with AKI which is not immediately life threatening, TDCs can be placed as the initial choice for vascular access. The National Kidney Foundation 2006 Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines also recommend NTDCs except when more prolonged vascular access (more than a week) for ongoing RRT is anticipated; TDCs should be used in this setting and also to replace NTDCs when such catheters have been in place for over a week (National Kidney Foundation Vascular Access 2006 Work Group., 2006).

Despite consensus-based guideline recommendations, there is increasing evidence that TDCs are associated with improved outcomes compared to NTDCs. These include fewer mechanical and infectious complications and better dialysis delivery. However, this evidence must be balanced by the feasibility and practicality of implementing a “TDC-first approach.”

8.3 Mechanical Complications

NTDCs tend to have lower blood flow rates than TDCs, potentially related to differences in internal diameter and tip design, leading to increased thrombosis and need for catheter adjustment and replacement (Kukavica., 2009; Ash., 2008; Weijmar., 2004., Mendu., 2017). This can shorten the time-period of delivery of IHD or CRRT, and therefore, impact the amount of dialysis delivered. In addition, catheter adjustment and replacement can lead to

patient discomfort and inconvenience.

In a prospective study of 31 patients on chronic haemodialysis, followed over a 36-month period and stratified according to catheter type, 24 catheter replacements were required for patients with NTDCs due to thrombosis during the study period, compared to two catheter replacements for patients with TDCs due to thrombosis over the same period (Kukavica., 2009). A study comparing retrospective outcomes of insertion of 272 TDCs and NTDCs over a 3 year period from 1997 to 2000 at a single academic teaching hospital showed that the rate of preliminary line removal per 1000 catheter days was far higher for NTDCs (19.5) than for TDCs (1.8) (Weijmar., 2004). Mechanical complications required the removal of 46% of NTDCs compared to 30% of TDCs while 45% NTDCs were removed due to inadequate blood flow, compared to 27% TDCs. Log-rank analysis of catheter survival curves showed better patency rates for TDCs compared to any NTDC subtypes. After correction for patient differences, the strongest risk factor for preliminary line removal was having an NTDC. When only jugular NTDCs were compared, the risk of preliminary removal for NTDCs remained almost 10-fold higher than for TDCs.

Given the relatively frequent use of TDCs for AKI requiring RRT at our institution and the paucity of published data on the subject, we performed a retrospective observational study at Brigham and Women's Hospital in 2016 comparing outcomes from NTDC vs TDC use for RRT in the ICU (Mendu., 2017). Mechanical complications were far more frequent with NTDCs compared to TDCs (65.7% vs 2.5%). The rate of overall complications, including positive blood cultures and mechanical complications, was 13.6-fold higher for NTDCs compared to TDCs. When the effect of multiple sticks was incorporated, the relative rate of overall complications increased further to 69-fold for NDTCs compared to TDCs.

8.4 Infectious Complications

TDCs have subcutaneous tunnels that increase the distance from the skin to the bloodstream and, therefore, theoretically lower the risk of associated catheter-related bloodstream infections. In fact, they do; NTDCs have up to a fivefold higher rate of infection

than TDCs (Vats., 2012; Raad., 1998). In addition to necessitating removal or replacement of catheters, infections require prolonged use of antibiotics, potentially with a prolonged hospital length of stay and the various complications of antibiotic therapy (eg, Clostridium difficile infection). All of this adds to the morbidity, mortality and expenditure attributable to vascular access for RRT.

Two prospective randomised studies investigated the effect of catheter tunnelling on catheter-related infections. Andrivet et al randomised 169 immunocompromised patients to subclavian NTDC or TDC placement and found that the frequency of catheter-related bacteraemia was lower for TDCs (2% with TDCs and 5% with NTDCs). The absence of statistical significance may be attributable to limited power of the study due to the small overall number of infections (Andrivet., 1994). In a larger study, Timsit et al randomised 241 critically ill patients who needed an internal jugular central venous catheter for greater than 48 hours to either TDC or NTDC placement (Timsit., 1996). They found a significant reduction in catheter-related sepsis for TDCs compared to NTDCs. Similarly, Weijmar et al compared retrospective outcomes of insertion of 272 TDCs and NTDCs and showed that the strongest risk factor for infection was having a NTDC (Weijmar., 2004).

Similarly, our prospective observational study of TDC vs NTDC use at Brigham and Women's Hospital found that significantly more blood cultures were drawn from NTDCs compared to TDCs, though the number of positive cultures drawn was not significantly different (Mendu., 2017).

8.5 Dialysis Delivery

Optimisation of the delivered dialysis dose in AKI can be affected by disruptions and reduction in overall treatment time as a result of access malfunction, low blood flow rates and high access pressures (Mehta., 2015). This can impact the ability to remove small- and middle-sized toxins and achieve effective fluid removal over the treatment time.

Only one single randomised, controlled, 34 patient trial has been reported in the literature examining the initial use of TDCs vs NTDCs for RRT in AKI. TDCs had a better ratio

of venous return pressure to catheter blood flow, leading to improved dialysis delivery (Klouche., 2007). However, only femoral vein catheters were utilised in this study, which are not the standard of care for dialysis vascular access in the ICU in the United States.

We found significantly better RRT delivery in patients with a TDC both with CVVH and IHD in our observational study of TDC vs NTDC use at Brigham and Women's Hospital (Mendu., 2017). Specifically, there was a 2.7-fold reduction in treatment interruptions for patients with TDCs on CVVH and significantly higher blood flow rates (368 vs 319 mL/min) for patients with TDCs on IHD. In summary, NTDCs were associated with significantly more infectious and mechanical complications compared to TDCs, and reduced delivery of effective RRT.

8.6 Feasibility

The rationale for existing consensus guidelines recommending initial NTDC placement for acute RRT is presumably due to the ease of arranging placement. NTDC insertion can be performed at the bedside, with little preparation or scheduling. NTDCs can also be easily removed, as they do not require cuff dissection. TDC insertion is clearly not without risk given cost and travel from the bedside to procedural areas, both for TDC insertion and removal. In addition, there are clear contraindications to TDC insertion, including hemodynamic instability, coagulopathy, and positive blood cultures.

However, given the evidence for improved performance and safety associated with TDC use, it is worth considering a “TDC-first” approach in cases where there are no contraindications. Our observational study showed that almost a third of patients obtained both a NTDC and TDC during their hospitalisation, with a mean duration of RRT of 17 days (interquartile range of 10-28) (Mendu., 2017). Therefore, a significant percentage of patients undergo at least two catheter placement procedures during hospitalisation, when likely one procedure would be sufficient. In one study involving TDCs for AKI-RRT, 80% of patients required RRT for greater than 1 week (Coryell., 2009). Similarly, in the Acute Renal Failure Trial Network study, 73% of patients requiring RRT had no recovery of kidney function by day 28 of hospitalization (VA/NIH Acute Renal Failure Trial Network., 2008).

8.7 A New Approach – "TDC-First"

Optimizing the delivery of RRT is key to ensuring its success in managing acid-base balance, uraemic burden, electrolyte, and fluid balance and outcomes. Since NTDCs are known to contribute to challenges in RRT delivery, the utility of TDC employment should be examined more closely. A TDC-first approach may be a means of optimizing first-line vascular access for AKI-RRT.

TDCs have traditionally been used to provide vascular access for patients with ESRD (Clark., 2016). We propose extending the role of TDCs to all suitable incident AKI patients. When such a "TDC first" approach is adopted, institutions will need to consider how to implement such a change. This includes improving scheduling availability as well as potentially expanding interventional nephrology training for fellows and faculty.

As part of our Standardised Clinical Assessment and Management Plan (SCAMP) observational study and subsequent trial at Brigham and Women's Hospital, we equipped providers with a decision support tool that aids daily assessment of AKI patients, their need for RRT and their potential recovery from AKI (Mendu., 2017). In addition, we have adopted a TDC-first approach through the SCAMP tool - this provides a clinical decision-making algorithm that favours use of TDCs as first-line access for RRT. As shown in Figure 8.1, the algorithm provides a list of relative contraindications to TDC insertion, including haemodynamic instability, bloodstream infection, severe coagulopathy, emergent need for access, and expected duration of RRT <1 week.

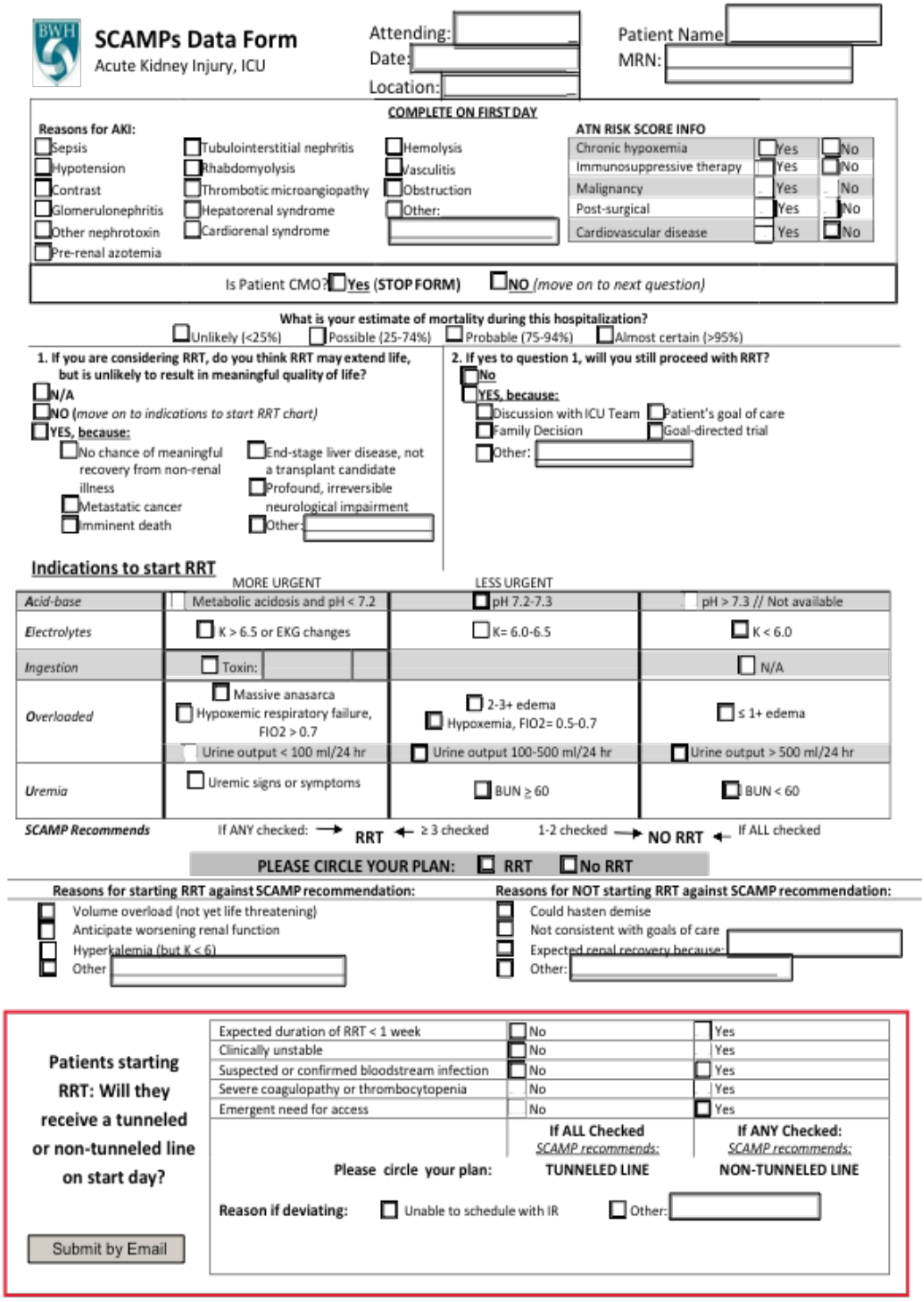
We have worked with our hospital to expand the availability of interventional radiology and nephrology services to facilitate increased access to TDC insertion and are tracking data on when TDC-first utilization is not adopted, despite recommendations. We support funding for continuing investigation in this area, specifically a pragmatic randomised controlled trial to assess the clinical outcomes and potential unintended consequences of using TDCs as first-line vascular access for AKI-RRT. We acknowledge that a "TDC-first" approach may represent a local preference within the US healthcare system and would therefore advocate

for use of an international multicentre trial to validate the generalisability of this approach in other healthcare settings.

8.8 Conclusions

In summary, several observational studies have demonstrated that TDCs for AKI requiring RRT are associated with a decreased risk of infection and thrombosis, and increased blood flow rates compared to NTDC access. A well-powered randomised controlled clinical trial has not yet been performed to provide level one evidence with respect to the feasibility and outcomes associated with a TDC-first approach to AKI-RRT access. In its absence, this choice remains an individualised one decided on a case-by-case basis. We, however, advocate for a TDC-first approach that extends the first-line use of TDCs to patients with AKI requiring RRT. We believe that such a "TDC-first" approach will facilitate RRT optimization and improve clinical outcomes for patients in addition to reducing resource utilisation and cost.

Figure 8.1 Tunneled dialysis catheter (TDC)-first algorithm (highlighted in red) as part of Brigham and Women's Hospital Acute Kidney Injury Standardised Clinical Assessment and Management Plan (BWH AKI-SCAMP).



SCAMPs Data Form
Acute Kidney Injury, ICU

Attending:
Date:
Location:
Patient Name
MRN:

COMPLETE ON FIRST DAY

Reasons for AKI:
- Sepsis
- Hypotension
- Contrast
- Glomerulonephritis
- Other nephrotoxin
- Pre-renal azotemia
- Tubulointerstitial nephritis
- Rhabdomyolysis
- Thrombotic microangiopathy
- Hepatorenal syndrome
- Cardiorenal syndrome
- Hemolysis
- Vasculitis
- Obstruction
- Other:

ATN RISK SCORE INFO

Chronic hypoxemia	Yes	No
Immunosuppressive therapy	Yes	No
Malignancy	Yes	No
Post-surgical	Yes	No
Cardiovascular disease	Yes	No

Is Patient CMO? **Yes (STOP FORM)** **NO** *(move on to next question)*

What is your estimate of mortality during this hospitalization?
Unlikely (<25%) Possible (25-74%) Probable (75-94%) Almost certain (>95%)

1. If you are considering RRT, do you think RRT may extend life, but is unlikely to result in meaningful quality of life?
- N/A
- NO *(move on to indications to start RRT chart)*
- YES, because:
  - No chance of meaningful recovery from non-renal illness
  - Metastatic cancer
  - Imminent death
  - End-stage liver disease, not a transplant candidate
  - Profound, irreversible neurological impairment
  - Other:

2. If yes to question 1, will you still proceed with RRT?
- No
- YES, because:
  - Discussion with ICU Team
  - Family Decision
  - Other:
  - Patient's goal of care
  - Goal-directed trial

Indications to start RRT

	MORE URGENT	LESS URGENT	
Acid-base	Metabolic acidosis and pH < 7.2	pH 7.2-7.3	pH > 7.3 // Not available
Electrolytes	K > 6.5 or EKG changes	K= 6.0-6.5	K < 6.0
Ingestion	Toxin:		N/A
Overloaded	Massive anasarca Hypoxemic respiratory failure, FIO2 > 0.7 Urine output < 100 ml/24 hr	2-3+ edema Hypoxemia, FIO2= 0.5-0.7 Urine output 100-500 ml/24 hr	≤ 1+ edema Urine output > 500 ml/24 hr
Uremia	Uremic signs or symptoms	BUN ≥ 60	BUN < 60

SCAMP Recommends If ANY checked: → **RRT** ← ≥ 3 checked 1-2 checked → **NO RRT** ← If ALL checked

PLEASE CIRCLE YOUR PLAN: RRT No RRT

Reasons for starting RRT against SCAMP recommendation:
- Volume overload (not yet life threatening)
- Anticipate worsening renal function
- Hyperkalemia (but K < 6)
- Other

Reasons for NOT starting RRT against SCAMP recommendation:
- Could hasten demise
- Not consistent with goals of care
- Expected renal recovery because:
- Other:

Patients starting RRT: Will they receive a tunneled or non-tunneled line on start day?

Expected duration of RRT < 1 week	No	Yes
Clinically unstable	No	Yes
Suspected or confirmed bloodstream infection	No	Yes
Severe coagulopathy or thrombocytopenia	No	Yes
Emergent need for access	No	Yes
	If ALL Checked *SCAMP recommends:*	**If ANY Checked:** *SCAMP recommends:*
Please circle your plan:	**TUNNELED LINE**	**NON-TUNNELED LINE**

Reason if deviating: Unable to schedule with IR Other:

Submit by Email

CHAPTER 9

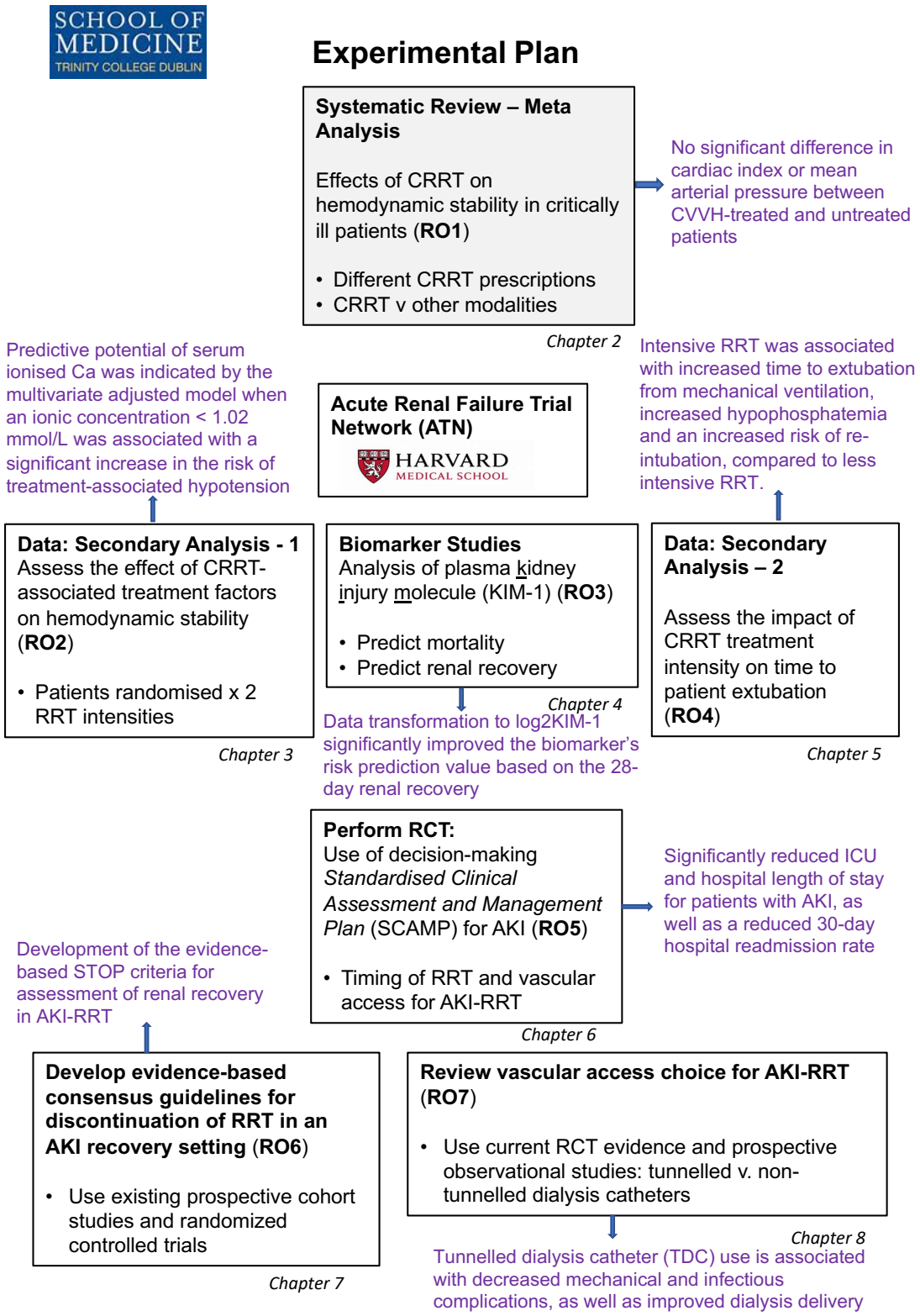
Conclusions

9.1 General discussion

Despite decades of research, the mainstay of treatment for severe acute kidney injury (AKI) in the critical care setting remains renal replacement therapy in the form of dialysis. Continuous renal replacement therapy (CRRT) poses the risk for unintended adverse events, which in general have been largely under-studied in critical care and nephrology; including depletion of phosphorus, amino acids, catecholamines and trace elements. CRRT also clears the circulation of medications, and dosing guidelines in general are not well established for CRRT.

Higher intensity CRRT has been studied as a potential therapeutic advance for the treatment of severe AKI by increasing middle molecule clearance, enhancing acid-base buffering and potentially reducing pro-inflammatory cytokines in the setting of sepsis and shock; however it has never been shown to have a mortality benefit. In thesis, I used prospectively collected clinical data from a multicentre randomised controlled trial to perform secondary statistical and biochemical analyses to assess the effect of intensity of CRRT prescription on the risk of adverse events, including haemodynamic instability and increased duration of mechanical ventilation due to treatment-induced hypophosphatemia. We also assessed the effects of timing of initiation and discontinuation of RRT for AKI on patient outcomes in a single-centre randomised controlled trial and performed a systematic review and meta-analysis on the effect of CRRT on hemodynamic instability in critically ill patients.

Figure 9.1 Summary of thesis findings based on the original experimental plan



9.2 A systematic review and meta-analysis of the effect of CRRT on haemodynamic outcomes in critically ill patients with AKI.

Haemodynamic derangement, including hypotension, on CRRT is common. Large retrospective cohort ICU studies have shown that up to 43% of patients experience new onset hypotension in the first hour after CRRT initiation (Akhoundi., 2015). Hypotension frequently leads to cessation of treatment. Patients who have difficulty in tolerating CRRT are more likely to die at an early stage.

We designed a systematic review and meta-analysis including both randomised controlled trials and prospective cohort studies which assessed the effect of CRRT on haemodynamic outcomes; in comparison either with other dialytic modalities or with CRRT at different prescriptions or in different patient populations. In total, 92 studies, including 41 randomised controlled trials and 51 prospective observational studies with a total sample size of 7759 patients, met inclusion criteria. Only 3 studies at maximum could be included in each meta-analysis due to significant variation in the haemodynamic parameters which were used as outcome measures. We found that there was no significant difference in cardiac index or mean arterial pressure between patients treated with CVVH compared to those who were not treated with CVVH; nor between patients treated with high volume CVVH compared to conventional volume CVVH. Mean arterial pressure was significantly lower for patients treated with CVVHD with lactate-buffered dialysate compared to those treated with CVVHD with bicarbonate-buffered dialysate. The risk of intradialytic hypotension was significantly higher for patients treated with CVVHDF compared to those treated with SLED. Similarly, the risk of hypotension was significantly higher for patients treated with CVVHDF compared to PD. However, there was significant heterogeneity present for all outcomes apart from the finding of reduced mean arterial pressure with CVVHD using lactate-buffered dialysate compared to bicarbonate-buffered dialysate. Given the small number of studies that could be included in each meta-analysis to produce a pooled effect estimate, we did not have sufficient power to perform subgroup analyses or meta regression to assess whether differences in baseline characteristics could account for the large amounts of heterogeneity observed.

Though limited by the small number of studies that could be included in each meta-analysis, as well as significant heterogeneity associated with the majority of pooled effect

estimates that were measured, Our systematic review therefore adds important information regarding the risk and incidence of hemodynamic instability as an adverse event associated with CRRT. A surprisingly small number of clinical trials in the CRRT literature have included haemodynamic adverse events as secondary outcomes. This has limited the ability of previous investigators to produce pooled estimates of the risk of the adverse events on CRRT. A recent Cochrane systematic review of intensity of RRT included only a maximum of 3 randomized controlled trials in its pooled estimates of adverse events on CRRT (Fayad., 2016). Our results are largely in keeping with those found in the Cochrane review and elsewhere in the literature which note that increased exposure to CRRT – either through intensity of dosing or early initiation on treatment - is associated with increased risk of arrhythmias, hypotension and electrolyte losses (the STARRT-AKI Investigators., 2020).

Our findings therefore emphasise the need for careful CRRT prescribing with the aid of evidence-based guidelines that support weight-based dosing to achieve a conventional intensity CRRT dose of 20-25 ml/kg/hour (KDIGO AKI Work Group., 2012) and that reserve intensive CRRT dosing for specific circumstances, e.g. post cardiac surgery where careful control of acidaemia may be needed in the setting of right ventricular failure, in order to minimise the risk of haemodynamic and other adverse events associated with higher intensity CRRT (Vidal., 2009). The increased risk of hypotension on CVVHDF in contrast to SLED or PD lends further credence to the potential utility of these dialytic modalities in the critical care setting for patients with AKI-RRT; where resources and education are available to support their wider use. However, our ability to draw conclusions are limited by the relatively small number of studies that could be pooled for meta-analysis in this systematic review. Large dedicated randomised controlled trials with haemodynamic and other adverse events as primary endpoints of CRRT treatment will be needed to determine the true incidence of haemodynamic adverse events according to CRRT prescription.

9.3 Predictors of CRRT-associated hypotension in the ICU

It is unclear whether modifiable CRRT treatment factors contribute to an increased risk of adverse haemodynamic outcomes in the critically ill. Hypocalcaemia is common in the setting of critical illness and can be exacerbated by electrolyte losses during CRRT

(Morimatsu., 2002). It may increase the risk of CRRT-associated hypotension due to its known effects on systemic vasodilation and reversible depression of left ventricular function (Jentzer., 2018; Newman., 2014). Similarly, faster rates of ultrafiltration may also give rise to increased risk of treatment-associated hypotension due to volume depletion and hemodynamic stress causing increased rates of arrhythmia and myocardial stunning (Silversides., 2014; Burton., 2009).

To test whether hypotension on CRRT is affected by CRRT treatment factors, we performed a secondary analysis of the ATN trial, a randomised controlled trial of intensive vs. less-intensive RRT (VA/NIH Acute Renal Failure Trial Network., 2008). We wished to assess whether modifiable CRRT treatment factors are associated with a higher risk of hypotension on CRRT treatment days.

In our post-hoc analysis of the ATN trial, 59.8% patients experienced severe hypotension while being treated with continuous renal replacement therapy. The majority of these events occurred on the first two days of treatment. In a multivariable adjusted model, a serum ionised calcium < 1.02 mmol/L was associated with a significant increase in the risk of treatment-associated hypotension, while CRRT treatment intensity, type of anti-coagulation used and CRRT blood flow rate did not have a significant effect on the risk of CRRT-associated hypotension, when analysed according to CRRT treatment days only. Therefore, while more than half of patients who receive CRRT experience severe hypotension while on treatment, there was no significant difference between intensive and less intensive CRRT groups with regard to the incidence of treatment-associated hypotension. Treatment dose therefore does not seem to be a significant risk factor for determining the rate of hemodynamic complications for CRRT patients. Similarly, we did not note any change in risk of hypotension associated with ultrafiltration rate in our multivariate adjusted model in this secondary analysis. From our baseline demographic data it was clear that illness severity scores such as APACHE II and SOFA, along with markers for organ failure including mechanical ventilation and oliguria, act as much more reliable predictors for who is more likely to experience hemodynamic instability on CRRT, rather than these aspects of the CRRT prescription.

A previous post-hoc secondary analysis of the ATN trial assessed the risk of mortality and renal recovery according to tertiles of ionised calcium during the trial and found that severe hypocalcaemia independently predicted mortality in patients with AKI requiring RRT, though there was no significant effect on renal recovery and hospital/ICU length of stay (Afshinnia., 2013). In addition to this, our secondary analysis has now shown that a serum ionised calcium < 1.02 mmol/L is associated with a significantly increased risk of treatment-associated hypotension, even when adjusted for baseline demographics, markers of illness severity and acidaemia in a multi-variable adjusted model. Further studies will be required to assess whether strict treatment targets for management of hypocalcaemia on CRRT will help to improve the risk of CRRT-associated hypotension in the future. Equally, I believe that updated CRRT guidelines should include management of hypocalcaemia; a practice that to date has been limited to citrate regional anti-coagulation protocols. However, dedicated randomised controlled trials will be needed to provide the highest evidence base for calcium treatment targets during CRRT.

9.4 Higher plasma KIM-1 is associated with increased 28-day mortality and decreased renal recovery in critically ill patients with AKI requiring RRT.

Kidney injury molecule 1 (KIM-1) is a transmembrane glycoprotein whose ectodomain is cleaved by matrix metalloproteinases and is present in the urine of humans and rodents after kidney proximal tubular injury (Han., 2002). It is up-regulated more than any other protein in the renal proximal tubules in the setting of AKI (Bonventre., 2009), and has important anti-inflammatory properties as part of the innate immune response, including phagocytosing apoptotic cells (Yang., 2015). Plasma KIM-1 increases during periods of renal ischaemia and can act as a sensitive marker for AKI severity (Sabbisetti., 2014). We hypothesised that higher baseline plasma KIM-1 levels prior to commencing RRT would be associated with increased mortality and decreased renal recovery in critically ill patients with severe AKI.

In this secondary analysis of the ATN trial, higher levels of plasma KIM-1 measured in critically ill patients with severe AKI at the time of randomisation (day 0) to intensive versus

less intensive RRT were associated with a decreased risk of 28-day renal recovery compared to lower levels of plasma KIM-1, when adjusted for components of the ATN mortality risk score in a multivariate model. Higher day 0 plasma KIM-1 levels were also associated with higher baseline eGFR, total SOFA and Cleveland Clinic Acute Renal Failure scores and with younger age. We also demonstrated that the addition of log2KIM-1 significantly improves risk prediction models for 28-day renal recovery.

Given that higher baseline plasma KIM-1 levels are also associated with increased risk of progression to ESRD, use of plasma KIM-1 may therefore allow us to predict which patients are more likely to require long-term renal replacement therapy, and could therefore help to guide patients and providers about decisions related to long-term RRT needs. The next step would be to design a multi-centre randomised controlled trial in which plasma KIM-1 measurement can be compared to standard of care in guiding providers about RRT decision-making and the appropriate allocation of resources for patients who are more likely to require renal support for an extended period of time.

9.5 Intensity of renal replacement therapy and duration of mechanical ventilation

Hypophosphatemia is a frequent complication during renal replacement therapy and may contribute to poor patient outcomes due to the critical role of phosphate in energy metabolism in every organ system (Santiago., 2009; Ratanarat., 2005; Schiffl., 2013). Hypophosphatemia can impair contractile properties of the diaphragm and may impair tissue oxygen extraction by reducing intracellular 2,3 diphosphoglycerate (2,3-DPG) concentrations (Sharma., 2015). Through a post-hoc analysis of a randomised controlled trial of intensive versus less intensive RRT in critically ill patients, we sought to assess the effect of RRT treatment intensity on the duration of mechanical ventilation as a potential adverse outcome of RRT-induced phosphate depletion.

We found that mechanically ventilated patients randomised to more-intensive RRT had longer duration of mechanical ventilation compared to those randomized to less-intensive RRT. Among patients who were successfully extubated initially, there was a significantly higher probability of re-intubation in those randomized to more more-intensive RRT. Notably,

during the study course, we found greater reduction in serum phosphate in the more-intensive treatment arm as compared with the less-intensive arm. Furthermore, within lowest baseline serum phosphate concentrations, there was less likelihood of being extubated in the more-intensive RRT compared to less-intensive RRT.

Several iatrogenic complications associated with higher dose of RRT have been cited in RRT literature (Mueller., 2003; RENAL Replacement Therapy Study Investigators., 2009). Nutritional status is a key prognostic factor in critically ill patients with AKI. It is plausible that nutritional status is compromised by depletion of vital nutrients with increased dose RRT, particularly in continuous therapies (Finkel., 2009). Our finding that mechanical ventilation was more prolonged in those on continuous RRT rather than intermittent RRT is consistent with the hypothesis that excessive losses through continuous RRT may be the underlying reason for our observed finding.

Excessive loss of phosphate during CVVH leading to hypophosphatemia has been reported as a complication in more than 10% of patients undergoing CRRT (Santiago., 2009; Ratanarat., 2005., RENAL Replacement Therapy Study Investigators., 2009). In the original report of the VA/NIH Acute Renal Failure Trial, hypophosphatemia was reported in 17.6% in those randomized to more-intensive RRT vs 10.9% in those randomised to less intensive RRT. Our findings, which were restricted to those on mechanical ventilation at the time of study initiation, showed similar results with a clear downward trend of phosphate over time. Although negative phosphate balance may be desirable earlier in the treatment of dialysis-requiring AKI (AKI-D), it may be detrimental to have continuous losses and negative phosphate balance during prolonged CRRT. Our findings were most pronounced in those with the lowest tertile of serum phosphate at baseline, further highlighting the importance of phosphate loss as a potential explanation of our findings.

Phosphate depletion is a plausible contributor to diaphragmatic and intercostal muscle weakness, which may account for our findings. Aubier., 1985 observed significant increase in trans-diaphragmatic pressure and response to phrenic nerve stimulation after correction of hypophosphatemia in 8 mechanically ventilated patients. In a prospective study of 23 patients with hypophosphatemia, Gravelyn., 1988 found respiratory muscle weakness (defined as reduction in maximal inspiratory pressure or maximal expiratory pressure) in 16 patients. In

addition, the mean initial respiratory pressures were significantly lower in the hypophosphatemic group compared to the control group with normal phosphate concentrations.

Other studies have also found that hypophosphatemia may be associated with worse pulmonary outcomes. In a single-center observational study with 321 AKI patients on continuous dialysis, Demirijian., 2011 found hypophosphatemia to be associated with higher incidence of prolonged respiratory failure requiring tracheostomy (OR 1.81; CI 1.07–3.08). In a single center prospective cohort study of 96 intensive care patients with AKI requiring RRT, Lim., 2017 found that hypophosphatemia during RRT was independently associated with prolonged mechanical ventilation (≥7 days) (adjusted OR 14.0, 95% CI 1.37- 143.90; $P = 0.03$). The finding that hypophosphatemia was associated with poor outcomes in patients on mechanical ventilation in observational studies may be confounded by other factors such as malnutrition. A key strength of our analysis is that we used randomized treatment assignment as a proxy for unregulated solute loss.

The implications of our study deserve to be highlighted, particularly given that more-intensive RRT continues to be frequently prescribed as evidenced by surveys from critical care physicians worldwide (Clark., 2017; Legrand., 2013). More-intensive RRT has not been shown to improve outcomes and may, as we have shown, have deleterious effects. If our findings are from excessive losses of small solutes such as phosphate, careful monitoring and repletion strategies should be implemented.

9.6 Block randomised implementation of a decision-making algorithm for renal replacement therapy initiation for AKI in comparison to standard care on AKI-related outcomes.

Delays in initiating RRT for AKI can result in serious preventable complications and even death (Bagshaw., 2009). However, initiating RRT carries procedural risks, including infection and bleeding, for patients who may recover renal function without requiring RRT. Recent randomized controlled trials have not conclusively shown a survival benefit of early versus late initiation of RRT for AKI (Gaudry., 2016; Zarbock., 2016; Barbar., 2018; the STARRT-AKI Investigators., 2020). To address uncertainty and variation in the care of

patients with AKI requiring RRT, we implemented a structured decision-making algorithm (Standardised Clinical Assessment and Management Plan or SCAMP) over a 13-month period for clinicians managing patients with AKI in the medical ICU (MICU) (Mendu., 2017). The AKI-SCAMP algorithm provided recommendations about optimal indications for initiating and discontinuing RRT on the basis of evidence-based clinical parameters. In this prior hypothesis-generating study, we found that patients whose clinicians adhered to the AKI-SCAMP recommendation to start RRT had lower in-hospital mortality and 60-day mortality, compared to those whose clinicians did not adhere to these recommendations. In particular, AKI-SCAMP recommendation adherence was associated with lower in-hospital mortality for patients with low disease severity, but no significant association was seen for patients with high disease severity.

In order to better understand the impact of the AKI-SCAMP on clinical outcomes such as 30-day, 60-day hospital mortality, hospital and ICU length of stay, and readmission, we implemented a block randomised design, which involved alternating the AKI-SCAMP with a "sham" SCAMP, which did not provide guidance on RRT initiation, but did include questions related to estimated risk of mortality and treatment futility. In this study we hoped to ascertain if there was utility in using the AKI-SCAMP regardless of adherence to the recommended algorithm, in a broad population of all ICU patients in our institution. We also introduced clinical decision-making related to tunnelled dialysis catheter (TDC) placement for AKI and the accuracy of physician estimation of mortality and futility.

The results of our block randomised controlled trial, involving patients in multiple medical and surgical ICUs in a single tertiary academic US centre found that use of a clinical decision support system in the form of a SCAMP did not impact the primary outcome of in-hospital, 30-day or 60-day mortality, but did result in a significantly reduced ICU and hospital length of stay for patients with AKI, as well as a reduced 30-day hospital readmission rate. We also found that patients in the AKI-SCAMP intervention group were less likely to receive RRT despite physician-perceived treatment futility than those in the control group. The ATN integer score was found to be a significantly better risk predictor for inpatient and 60-day mortality in comparison to physician-predicted mortality.

There are few interventions that have been shown to improve outcomes for patients with AKI. The increased mortality and length of stay associated with AKI remains staggeringly high – with a 6.5 fold increase in mortality and a 3.5 fold increase in hospital length of stay reported by Chertow et al in recent years (Chertow., 2005). Various studies have acknowledged the impact of SCAMPs on increasing clinicians' rate of compliance with best evidence-based practices for acute and chronic diseases and on reducing medical costs for chronic disease by reducing the unnecessary use of resources (Farias., 2012; Verghese., 2012). SCAMPs have been shown to improve patient outcomes, such as in a study of catheterization management for aortic stenosis in children, in which the rate of optimal results with balloon dilation significantly improved post introduction of a SCAMP (Porras., 2014). In addition, SCAMPs are associated with increased provider satisfaction ratings (Farias., 2011).

In this AKI-SCAMP block randomised controlled trial, there was no significant effect of the AKI-SCAMP clinical decision support tool on risk of mortality compared to controls. This is in contrast to the 2017 AKI-SCAMP observational study (Mendu., 2017), which found a significant reduction in patient mortality associated with adherence to the AKI-SCAMP clinical decision support tool. However, in the original manuscript there was a more limited population, focused on the MICU of Brigham and Women's Hospital, which did not encompass the mixed medical, surgical, cardiothoracic and neurological populations that were included in the randomised controlled trial. There was a much higher rate of AKI-SCAMP non-adherence at 57% in the observational study, compared to an AKI-SCAMP non-adherence rate of just 8.5% in this clinical trial. This likely led to fewer delays in initiating RRT when needed, which may have reduced the impact of the AKI-SCAMP on mortality. Our observational study also did not have a control group for comparison, and it utilised both nephrology fellows and attendings, as opposed to focusing specifically on critical care nephrology attendings.

Our AKI-SCAMP randomised trial did show a significant reduction in ICU and hospital length of stay; as well as in 30-day hospital readmission rates; acknowledging however that these were all secondary outcomes of the trial. Use of the AKI-SCAMP may have led to more judicious overall use of RRT and increased consideration of timely cessation of RRT when appropriate. Reduced use of RRT as a resource may have accounted for shortened hospital

and ICU length of stay, and potentially reduced readmission rates due to reduced risk of complications associated with shortened exposure to this treatment modality and its associated procedural risks. Fewer patients in the AKI-SCAMP intervention arm also received RRT in the setting of physician-perceived treatment futility, which shows potentially more judicious use of RRT associated with the AKI-SCAMP intervention.

We also evaluated physician mortality prediction in the AKI-SCAMP trial and found that the ATN integer score performed better than “best guess” physician-predicted mortality in predicting both inpatient and 60-day mortality. The ATN integer score was first derived by Demirjian et al using data from the Veteran Affairs/National Institutes of Health Acute Renal Failure Trial Network study to identify 21 independent predictors of 60-day mortality which outperformed existing generic and disease-specific scoring systems when applied in a logistic regression model (Demirjian., 2011; VA/NIH Acute Renal Failure Trial Network., 2008). These findings have subsequently been replicated in other large retrospective and prospective cohort studies (Bolanos., 2015; Carvalho., 2018). The accuracy of physician predicted risk of mortality in AKI has varied significantly in different studies. Allegretti et al. studied physician, nurse and patient/healthcare proxy perceptions of AKI-RRT prognosis and found that only 44% of physicians identified rates of survival that were consistent with the published literature (Allegretti., 2015). In a study of end-stage renal disease patients, Wachterman et al. found that chronic hemodialysis patients were significantly more optimistic in their estimates of 1-year survival than their nephrologists (Wachterman., 2013). One approach that has been advocated for is training physicians to consider critical prognostic information in clinical decision-making by combining quantitative risk prediction tools with qualitative judgement, to facilitate better patient outcomes (Gill., 2012).

A larger multi-centre randomised controlled trial, involving ICUs in multiple hospitals in diverse settings, would be ideal to validate the results of this study and to provide further generalisability. However, given the compelling results both from the AKI-SCAMP observational study and this randomised controlled trial, I feel that there is substantial evidence to support use of AKI-SCAMP as a clinical decision support tool to guide decision-making regarding RRT initiation, in order to improve patient outcomes and reduce costs associated with length of stay, readmission and unnecessary treatment in cases of futility.

9.7 Development of consensus guidelines for discontinuation of AKI-RRT in the setting of renal recovery

The delivery of renal replacement therapy (RRT) for patients with acute kidney injury (AKI) is extremely variable and based primarily on empiricism and local institutional practice (Mehta., 2004; Uchino., 2005; Ricci., 2006). In particular, there is little consensus regarding timing for discontinuation. The multiplicity of RRT discontinuation criteria used in high-quality multicentre RCTs evinces the need for consensus. Discrepant threshold criteria make it difficult to evaluate and compare outcomes from these trials and highlight the need to consolidate discontinuation criteria.

The criteria for defining "successful" discontinuation are also not clearly established. Studies to date examining the utility of various criteria on predicting the successful discontinuation of RRT (i.e. RRT does not need to be restarted and the patient experiences some degree of renal recovery) have focused on two types of criteria: (a) urine volume over time and (b) renal creatinine clearance. Some have incorporated concomitant diuretic therapy in their criteria. Examining the available evidence to date from randomised controlled trials and prospective cohort studies that have assessed renal recovery with differing cut-off criteria as part of their study protocol, I found that the best current evidence available supports a native urine output (urine OutPut) > 400 ml/24 hours without diuresis or > 2000 ml/24 hours with diuresis and a 24 hour urinary creatinine clearance clearance > 15 ml/min (Timed creatinine clearance), in conjunction with a clinical examination (clinical Status) that supports cessation of RRT (i.e. the absence of volume overload and uraemic symptoms). I have dubbed these putative guidelines the "STOP criteria". Validation of these criteria in a prospective randomised controlled will be necessary to increase the grade of evidence which supports these criteria but I believe that this synthesis of the currently available literature is important in providing more specific guidance for care-givers to support their current decision-making regarding cessation of AKI-RRT.

Given the sparse literature on this topic, it is clear that there are no consensus criteria regarding RRT discontinuation. It is vital to establish objective criteria to guide clinical decision-making and inform study design. The rate of urine volume, creatinine clearance, and subjective clinical criteria are considerations in this proposed "STOP" criteria framework. A

prospective clinical trial that compares disparate clinical criteria (specifically, urine output and creatinine clearance) is required to establish clear guidelines for RRT discontinuation. Establishment of "STOP" criteria is a necessary step in ensuring that RRT discontinuation decision-making is evidence based, and could potentially improve outcomes by limiting RRT duration, delayed renal recovery, and hospital length of stay.

9.8 Optimising vascular access choice for AKI-RRT

RRT in the setting of AKI is provided by either tunnelled or non-tunnelled dialysis catheters (TDCs or NTDCs), used immediately after insertion. NTDCs are typically placed at bedside in the internal jugular or femoral vein by either nephrologists or intensivists; dynamic ultrasound guidance (as recommended by professional societies) reduces the risk of insertion-related complications (KDIGO AKI Work Group., 2012; Troianos., 2012., Pittiruti., 2009; Lamperti., 2012; Bodenham., 2016; Bouaziz., 2015., Rabindranath., 2011). TDCs are typically placed in the right internal jugular vein by interventional radiologists, interventional nephrologists, or vascular surgeons in procedural areas, with the aid of both ultrasound and fluoroscopic guidance.

Kidney Disease: Improving Global Outcomes (KDIGO) guidelines suggest using NTDCs rather than TDCs for vascular access in AKI (level of evidence, 2D), primarily for logistical reasons—namely, ease of insertion and timeliness (KDIGO AKI Work Group., 2012). However, the guidelines state that for patients with AKI which is not immediately life threatening, TDCs can be placed as the initial choice for vascular access. The National Kidney Foundation 2006 Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines also recommend NTDCs except when more prolonged vascular access (more than a week) for ongoing RRT is anticipated; TDCs should be used in this setting and also to replace NTDCs when such catheters have been in place for over a week (National Kidney Foundation Vascular Access 2006 Work Group., 2006).

Despite consensus-based guideline recommendations, there is increasing evidence that TDCs are associated with improved outcomes compared to NTDCs. These include fewer mechanical and infectious complications and better dialysis delivery. However, this evidence

must be balanced by the feasibility and practicality of implementing a "TDC-first approach."

My narrative review of the literature, including a prospective cohort study performed by our research group at Brigham and Women's Hospital in 2017 (Mendu., 2017) consistently shows that TDC use is associated with decreased mechanical and infectious complications, as well as improved dialysis delivery by comparison with use of NDTCs. Given the evidence for improved performance and safety associated with TDC use, it is worth considering a "TDC-first" approach in cases where there are no contraindications. Our observational study showed that almost a third of patients obtained both a NTDC and TDC during their hospitalisation, with a mean duration of RRT of 17 days (interquartile range of 10-28) (Mendu., 2017). Therefore, a significant percentage of patients undergo at least two catheter placement procedures during hospitalisation, when likely one procedure would be sufficient. In one study involving TDCs for AKI-RRT, 80% of patients required RRT for greater than 1 week (Coryell., 2009). Similarly, in the Acute Renal Failure Trial Network study, 73% of patients requiring RRT had no recovery of kidney function by day 28 of hospitalization (VA/NIH Acute Renal Failure Trial Network., 2008). A well-powered randomized controlled clinical trial has not yet been performed to provide level one evidence with respect to the feasibility and outcomes associated with a TDC-first approach to AKI-RRT access. In its absence, this choice remains an individualised one decided on a case-by-case basis. I, however, advocate for a TDC-first approach that extends the first-line use of TDCs to patients with AKI requiring RRT, in the belief that such a "TDC-first" approach will facilitate RRT optimisation and improve clinical outcomes for patients in addition to reducing resource utilisation and cost.

9.9 Future directions

The studies performed as part of this thesis describe numerous ways in which use of CRRT can lead to adverse events. In some cases, the quality of the existing evidence for this can vary in quality or be indirect in nature. My systematic review and meta-analysis was largely

composed of observational studies where haemodynamic outcomes were assessed as secondary outcomes or adverse events during the course of study, rather than as well-powered primary end-points of interest. Further dedicated CRRT clinical trials which assess haemodynamic outcomes as a primary end-point are needed to add to the quality of the evidence that exists in this field. My secondary analyses of the ATN clinical trial which looked at haemodynamic outcomes from the trial according to CRRT treatment factors, patient outcomes according to levels of renal tubular biomarkers at the start of the trial and the effect of intensity of RRT on duration of mechanical ventilation attempted to use prospectively collected controlled multicentre clinical trial data to bolster the quality of the existing evidence for the incidence of and risk factors for adverse events on CRRT. Again, dedicated clinical trials are the ideal solution to provide the highest level of evidence to support these findings, but equally I believe that these secondary analyses, in conjunction with the existing evidence, should be used to objectively reassess our existing clinical guidelines for management and dosing of CRRT.

The translational role of renal biomarkers in prognosticating patient outcomes in AKI or in helping to determine treatment strategies requires further elucidation. My aim was to further characterise the clinical utility of plasma KIM-1 as a biomarker of ischemic renal tubular injury and I would like to go on to validate this in other critically ill AKI patient populations; particularly looking at cross-talk between markers of AKI and other organ failure such as acute lung injury. My putative hypothesis would address whether plasma KIM-1 may have a further role in predicting non-renal organ failure in critical illness in addition to the patient outcomes which we have described in our secondary analyses of the ATN trial.

With regard to the STOP criteria which we have produced as guidelines for discontinuation of AKI-RRT in the setting of potential renal recovery, I would like to prospectively validate these criteria in a large population of mixed ICU patients – either in a prospective cohort study or as a clinical trial utilising two different cut-off criteria for urine output for discontinuation of RRT. The results of our AKI-SCAMP clinical trial are very promising with regard to the impact of use of the AKI-SCAMP decision-making algorithm on ICU and hospital length of stay as well as readmission rates. Given that this was a single centre randomised controlled trial, it ideally should be validated in other centres to assess its

generalisability in other ICU populations. Similarly, we have gathered a lot of compelling observational evidence to support increased use of TDCs as first-line access for AKI-RRT, but again a dedicated trial of TDC vs NTDC for first-line dialysis access for AKI is really needed to provide a higher grade of evidence beyond the recommendations that guidelines can support at present.

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