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Preventive Strategies for Acute Kidney Injury among Patients Undergoing Abdominal Aortic Aneurysm Repair

Michaela Fernandes, *The University of Western Ontario*

Supervisor: Dubois, Luc, *The University of Western Ontario*
Co-Supervisor: Garg, Amit X, *The University of Western Ontario*
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Abstract

Strategies for preventing acute kidney injury (AKI) in patients undergoing abdominal aortic aneurysm (AAA) repair were explored in a secondary data analysis of 601 patients from a randomized controlled trial (RCT). Bivariate analyses identified an association between intraoperative hypotension and postoperative AKI and suggested IV fluids as the best treatment option over inotropes/vasopressors which increased the odds of AKI (OR_{crude}=2.5 95%CI 1.2-5.0), however, our multivariable analysis was non-significant ($OR_{adjusted}$=1.7 95%CI 0.8-3.7). Further analysis found angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker use within 24 hours prior to repair were not associated with postoperative AKI ($OR_{adjusted}$=1.3 95%CI 0.8-2.2). Our systematic review of RCT literature failed to identify any definitive evidence for effective preventive strategies, and our meta-analysis of 6 RCTs analyzing remote-ischemic preconditioning showed no statistically significant difference (OR 1.2 95%CI 0.4-3.9). Large, multi-centre RCTs are needed to identify preventive strategies for AKI after AAA repair.

Keywords

Abdominal aortic aneurysm, endovascular repair, open repair, acute kidney injury, prevention.

Summary for Lay Audience

An abdominal aortic aneurysm (AAA) is the ballooning of the aorta in the abdomen caused by a weakening in the walls of the vessel. Aneurysms can occur in different locations along the aorta and can negatively affect the supply of blood to the kidneys. The repair of an AAA can cause stress to the kidneys due to the procedure and/or different drugs resulting in acute kidney injury (AKI), a significant complication associated with AAA repair. AKI is defined as an abrupt decline in kidney function. This thesis explores potential strategies for preventing AKI in patients undergoing AAA repair. We explored this in a secondary data analysis of 601 patients from a randomized controlled trial (RCT). Statistical analyses identified an association between low blood pressure during surgery and postoperative AKI. Analyses of the treatments of the low blood pressure during surgery suggested IV fluids as the possible best treatment option over inotropes/vasopressors which increased the odds of patients developing AKI after surgery, however further analysis was non-significant, so the evidence is unclear. Drugs to treat high blood pressure have been thought to affect the results of patients undergoing AAA repair and there are conflicting opinions about whether they should be stopped before surgery or not. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers are drugs used to treat high blood pressure and if taken close to surgery, they may increase the risk of low blood pressure during surgery which is associated with AKI. Our analysis found angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers taken within 24 hours prior to repair were not associated with postoperative AKI. We conducted a systematic review and meta-analysis of RCT literature, but we did not identify any conclusive evidence for effective preventive strategies. Future research needs to be conducted to identify preventive strategies for AKI after AAA repair using randomized trials.

Co-Authorship Statement

The study and systematic review presented here in an integrated-article style thesis were designed and executed by Michaela Fernandes. Dr. Luc Dubois was the primary supervisor and was involved in all aspects of this work. Dr. Amit Garg was the co-supervisor and Dr. Neil Klar was a thesis committee supervisor and both were involved in study design and provided comprehensive feedback. A version of the systematic review and meta-analysis manuscript is in preparation for submission and each co-author critically appraised the manuscript and provided important feedback for manuscript revision. Melissa Majoni, co-author, was an invaluable second reviewer for study screening, risk of bias assessment and data extraction.

Dedication

To my parents for their unwavering support and for instilling in me a great passion for research, my grandparents, whose sacrifices made this all possible and to Meghan, Bianca, Nicole & Brady for their endless love. To my Mai, my 96-year-old dynamo of a great-grandmother who received a AAA repair 20 years ago at Victoria Hospital by Dr. DeRose.

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List of Abbreviations

AAA	Abdominal aortic aneurysm
ACE	Angiotensin-converting enzyme
AKI	Acute kidney injury
AKIN	Acute kidney injury network
ARB	Angiotensin II receptor blocker
CAD	Coronary artery disease
CCRBT	Cochrane collaboration risk of bias tool
CDE	Controlled direct effect
CHF	Congestive heart failure
CI	Confidence interval
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
CrCl	Creatinine clearance
CVE	Cerebrovascular event
CVP	Central venous pressure
DM	Diabetes mellitus
eGFR	Estimated glomerular filtration rate
EVAR	Endovascular aneurysm repair
GFR	Glomerular filtration rate
hANP	Human atrial natriuretic peptide
HES	Hydroxyethyl starch
HHS	Hamilton health sciences
HR	Hazard ratio

HSC	Health sciences centre
HSN	Health sciences north
HTN	Hypertension
ICTRP-WHO	International clinical trials registry platform – World Health Organization
IV	Intravenous
KDIGO	Kidney disease improving global outcomes
LHSC	London health sciences centre
MAP	Mean arterial pressure
NDE	Natural direct effect
NIE	Natural indirect effect
OH	Ottawa hospital
OR	Odds ratio
PLC	Peter Lougheed centre
RAAS	Renin aldosterone-angiotensin system
RAS	Renin angiotensin system
RCT	Randomized controlled trial
RIFLE	Risk, Injury, Failure, Loss, End-stage renal disease
RIPC	Remote ischemic preconditioning
RR	Risk ratio
RRT	Renal replacement therapy
SAS	Statistical analysis software
SBH	St. Boniface hospital
SBP	Systolic blood pressure

SCr	Serum creatinine
SD	Standard deviation
SMH	St. Michael's hospital
TE	Total effects
UAH	University of Alberta health

Chapter 1

1 Introduction

1.1 Thesis Rationale

An abdominal aortic aneurysm (AAA) is a widening or ballooning of the aorta to a diameter ≥ 3.0cm.[1,2] This condition is often asymptomatic and the risk of rupture increases as the aneurysm enlarges, typically over 5-5.5cm in size. AAAs are repaired to prevent rupture using either an open or endovascular (EVAR) approach. A common postoperative complication among AAA repair patients is acute kidney injury (AKI). The incidence of postoperative AKI following EVAR ranges from 1% to 19% ; [3,4–6] while the incidence after open repair ranges from 2% to 29.9%.[4,7,8–17] AKI is an abrupt decline in kidney function and tends to be underdiagnosed due to varying definitions.[18,19] AKI development postoperatively is associated with significant morbidity, mortality, length of hospitalization and hospital costs.[18,20–24] Potential therapeutic targets for the prevention of AKI following AAA repair have not been clearly elucidated. Understanding potential risk factors is fundamental to proposing preventive strategies. There remains no proven method to prevent AKI following AAA repair and it remains a challenging unsolved clinical problem.

1.2 Thesis Objectives

Objective 1) To explore potential strategies for the prevention of AKI in patients undergoing AAA repair

1a) To examine the association of angiotensin-converting enzyme inhibitor and/or angiotensin II receptor blocker use within 24 hours of AAA repair with AKI (Chapter 3)

1b) To examine the association of intraoperative hypotension (SBP < 100mmHg) and its associated treatments during AAA repair with AKI (Chapter 3)

1c) To identify and evaluate the preventive strategies for AKI tested in randomized controlled trials available in published literature. (Chapter 4)

1.3 Thesis Outline

The goals of this thesis are to summarize the existing high-quality evidence supporting potential therapeutic strategies to prevent AKI after AAA repair; and to conduct a secondary data analysis of the largest randomized controlled trial (RCT) conducted on this topic (curcumin trial – believed to possess anti-inflammatory and anti-oxidant properties) looking for novel therapeutic strategies associated with an altered risk of AKI.[25]

This thesis includes 5 chapters. Chapter 1 is a statement of objectives and brief rationale for the overall work. The relevant literature concerning abdominal aortic aneurysm repair, acute kidney injury and potential therapeutic targets for prevention of postoperative AKI among AAA repair patients is reviewed in chapter 2. Chapter 3 details the results of a secondary data analysis of the curcumin trial data looking for the potential effects of intraoperative blood pressure management and preoperative use of ACE inhibitors/ARBs on the odds of AKI after AAA repair. The analyses reported in chapter 3 are then placed into a broader context in chapter 4 which includes the methods and results of a systematic review and meta-analysis evaluating the high-quality literature looking at preventive strategies for AKI after AAA repair. Finally, chapter 5 outlines the overall conclusions of the work, limitations, and suggested future directions.

1.4 References

1. Kuivaniemi H, Ryer EJ, Elmore JR, Tromp G. Understanding the pathogenesis of abdominal aortic aneurysms. Expert Rev Cardiovasc Ther. 2015;13(9):975–87.

2. Kapila V, Jetty P, Wooster D. The Canadian Society for Vascular Surgery 2018 screening for abdominal aortic aneurysms in Canada: Review and position statement from the Canadian Society of Vascular Surgery. Can Soc Vasc Surg. 2018;(July).

3. Saratzis AN, Goodyear S, Sur H, Saedon M, Imray C, Mahmood A. Acute kidney injury after endovascular repair of abdominal aortic aneurysm. J Endovasc Ther. 2013;20(3):315–30.

4. Wald R, Waikar SS, Liangos O, Pereira BJG, Chertow GM, Jaber BL. Acute renal failure after endovascular vs open repair of abdominal aortic aneurysm. J Vasc Surg. 2006;43(3):466.

5. Abraham CZ, Chuter TAM, Reilly LM, Okuhn SP, Pethan LK, Kerlan RB, et al. Abdominal aortic aneurysm repair with the Zenith stent graft: Short to midterm results. J Vasc Surg. 2002;36(2):217–25.

6. Prinssen M, Verhoeven ELG, Buth J, Cuypers PWM, van Sambeek MRHM, Balm R, et al. A randomized trial comparing conventional and endovascular repair of abdominal aortic aneurysms. N Engl J Med. 2004;351(16):1607–18.

7. Johnston KW. Multicenter prospective study of nonruptured abdominal aortic aneurysm. Part II. Variables predicting morbidity and mortality. J Vasc Surg. 1989;9(3):437–47.

8. Greenberg RK, Chuter TAM, Lawrence-Brown M, Haulon S, Nolte L, Investigators Z. Analysis of renal function after aneurysm repair with a device using suprarenal fixation (Zenith AAA Endovascular Graft) in contrast to open surgical repair. J Vasc Surg. 2004;39(6):1219–28.

9. Adriaensen MEAPM, Bosch JL, Halpern EF, Myriam Hunink MG, Gazelle GS. Elective

endovascular versus open surgical repair of abdominal aortic aneurysms: Systematic review of short-term results. Radiology. 2007;224(3):739–47.

10. Chen JC, Hildebrand HD, Salvian AJ, Taylor DC, Strandberg S, Myckatyn TM, et al. Predictors of death in nonruptured and ruptured abdominal aortic aneurysms. J Vasc Surg. 1996;24(4):613–4.

11. Hertzer NR, Mascha EJ, Karafa MT, O'Hara PJ, Krajewski LP, Beven EG. Open infrarenal abdominal aortic aneurysm repair: The Cleveland Clinic experience from 1989 to 1998. J Vasc Surg. 2002;35(6):1145–54.

12. Hua HT, Cambria RP, Chuang SK, Stoner MC, Kwolek CJ, Rowell KS, et al. Early outcomes of endovascular versus open abdominal aortic aneurysm repair in the National Surgical Quality Improvement Program-Private Sector (NSQIP-PS). J Vasc Surg. 2005;41(3):382–9.

13. Dariane C, Coscas RR, Boulitrop C, Javerliat I, Vilaine E, Goeau-Brissonniere O, et al. Acute kidney injury after open repair of intact abdominal aortic aneurysms. Ann Vasc Surg. 2017;39(November 2016):294–300.

14. Shahverdyan R, Majd MP, Thul R, Braun N, Gawenda M, Brunkwall J, et al. F-EVAR does not impair renal function more than open surgery for juxtarenal aortic aneurysms: single centre results. Eur J Vasc Endovasc Surg. 2015;50(4):432–41.

15. Castagno C, Varetto G, Quaglino S, Frola E, Scozzari G, Bert F, et al. Acute kidney injury after open and endovascular elective repair for infrarenal abdominal aortic aneurysms. J Vasc Surg. 2016;64(4):928+.

16. Tang Y, Chen J, Huang K, Luo D, Liang P, Feng M, et al. The incidence, risk factors and in-hospital mortality of acute kidney injury in patients after abdominal aortic aneurysm repair surgery. BMC Nephrol. 2017;18(1):184.

17. Surowiec SM, Davies MG, Fegley AJ, Tanski WJ, Pamoukian VN, Sternbach Y, et al. Relationship of proximal fixation to postoperative renal dysfunction in patients with normal serum creatinine concentration. J Vasc Surg. 2004;39(4):804–10.

18. KDIGO. Clinical practice guideline for acute kidney injury (AKI). Kidney Int Suppl. 2012;2(1):4.

19. Hobson C, Lysak N, Huber M, Scali S, Bihorac A. Epidemiology, outcomes, and management of acute kidney injury in the vascular surgery patient. J Vasc Surg. 2018;68(3):916–28.

20. Saratzis A, Shakespeare J, Jones O, Bown MJ, Mahmood A, Imray CHE. Pre-operative functional cardiovascular reserve is associated with acute kidney injury after intervention. Eur J Vasc Endovasc Surg. 2017;53(5):717–24.

21. Tang Y, Chen J, Huang K, Luo D, Liang P, Feng M, et al. The incidence, risk factors and in-hospital mortality of acute kidney injury in patients after abdominal aortic aneurysm repair surgery. BMC Nephrol. 2017;18(1):184.

22. Boyle JR. Preventing EVAR Associated acute kidney injury: The optimal strategy remains elusive. Eur J Vasc Endovasc Surg. 2018;55(5):657.

23. Becquemin JP, Chemla E, Chatellier G, Allaire E, Mellière D, Desgranges P. Perioperative factors influencing the outcome of elective abdominal aorta aneurysm repair. Eur J Vasc Endovasc Surg. 2000;20(1):84–9.

24. Zabrocki L, Marquardt F, Albrecht K, Herget-Rosenthal S. Acute kidney injury after abdominal aortic aneurysm repair: current epidemiology and potential prevention. Int Urol Nephrol. 2018;50(2):331–7.

25. Garg AX, Devereaux PJ, Hill A, Sood M, Aggarwal B, Dubois L, et al. Oral curcumin in elective abdominal aortic aneurysm repair: A multicentre randomized controlled trial. Can Med Assoc J. 2018;190(43):E1273–80.

Chapter 2

2 Literature Review

This chapter will include a review of the literature relating to abdominal aortic aneurysm repair, acute kidney injury, ACE inhibitors and ARBs, intraoperative hypotension and preventive strategies for AKI among AAA repair patients.

2.1 Abdominal Aortic Aneurysm Repair

The widening or ballooning of the aorta ≥ 3.0cm in diameter is an abdominal aortic aneurysm (AAA).[1,2] AAAs are prevalent among 0.0% to 12.5% of men, and 0.0% to 5.2% of women.[3] Among men over the age of 65, 1% of deaths are due to AAAs and are therefore responsible for over 175,000 deaths worldwide.[3] The major risk factors associated with AAAs are smoking, hypertension, and family history.[1,2] The purpose of electively treating AAAs is to prevent rupture of the aneurysm and the associated 80% mortality rate.[1–3] AAA can be treated using either an open repair or an endovascular repair (EVAR). Open repair is an invasive procedure requiring the surgeon to enter the abdominal cavity and hand-sew an interposition graft, thus excluding the aneurysm from circulation; while the endovascular repair or EVAR consists of minimally invasive surgery with the placement of a stent graft through the femoral artery to exclude the aneurysm from circulation.[1,2] Reports of perioperative mortality in elective open AAA repair patients ranges from 1 – 4% and major adverse events are reported in 15 - 30% of patients who tend to have more comorbidities compared with EVAR patients.[1] In a meta-analysis of four RCTs comparing patients who received EVAR and those who received an open repair, 30 day in hospital mortality was significantly lower among EVAR patients (1.4% vs. 4.2% $P<0.0001$, OR

0.3 95% CI 0.2 to 0.6).[4] There appears to be an advantage regarding short-term mortality among EVAR patients compared with open repair patients, further confirmed in four independent systematic reviews and/or meta-analyses.[4–7] One of the reviews of the short term results from AAA repair found that EVAR results in less blood loss, shorter hospital stays, lower 30 day mortality and complication rates compared with open repair patients.[7] Although EVAR has short-term benefits when compared to open repair; it does have some long-term disadvantages. In the long-term results of the EVAR-1 trial, the largest RCT of open vs EVAR in AAA repair patients, reintervention rates were higher among EVAR patients, as was long-term mortality.[8] These results are confirmed in four independent systematic reviews which found higher long-term all-cause mortality, reintervention and secondary rupture rates in EVAR patients when compared with open repair patients.[4,5,9,10] The inferior long-term results after EVAR are largely attributed to the loss of aortic seal with secondary aneurysm sac perfusion and risk of secondary rupture and need for reintervention. Acute kidney injury (AKI) is a major adverse outcome following AAA repair and occurs frequently following either open or endovascular aortic aneurysm repair. It is one of the most common postoperative complications following AAA repair, but tends to be underdiagnosed due to variable definitions of AKI.[11]

2.2 Acute Kidney Injury

2.2.1 Definition and classification of AKI

Acute kidney injury is the abrupt decline in kidney function.[12] Varying definitions have been used over the years including different sets of criteria and sometimes arbitrary clinical thresholds. These inconsistencies led to the establishment of the KDIGO criteria, the Kidney Disease Improving Global Outcomes criteria for AKI definition and classification.[12] Using the

KDIGO criteria, AKI is defined as any of the following: increase in serum creatinine (SCr) by 0.3 mg/dl (26.5 μmol/l) within 48 hours; or increase in SCr to 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or urine volume 0.5 ml/kg/h for 6 hours.[12] Glomerular filtration rate (GFR) is the most widely accepted and most useful measure of kidney function such that SCr and urine output can be used as surrogate measures for changes in GFR.[12] Previous consensus criteria include the Risk, Injury, Failure, Loss, End-Stage Kidney Disease (RIFLE) and Acute Kidney Injury Network (AKIN) criteria have been further optimized and combined to form the KDIGO criteria.[12–14]

AKI is classified according to 3 stages of increasing severity using SCr and/or urine output: the first stage is defined as an increase of 1.5-1.9 times baseline SCr or 0.3 mg/dl (26.5 μmol/l) increase in SCr; or urine volume 0.5 ml/kg/h for 6-12 hours. The second stage is defined as an increase of 2.0 – 2.9 times baseline; or urine output of 0.5 ml/kg/h for 12 hours. The third stage is defined as: an increase of 3.0 times baseline SCr, or increase in SCr to 4.0 mg/dl (353.6 μmol/l) or initiation of renal replacement therapy, or in patients < 18 years: decrease in eGFR to <35 mL/min per 1.73 m_2; or urine output of 0.3 ml/kg/h for 24 hours or anuria for 12 hours.[12]

2.2.2 Mechanisms of AKI

As outlined in the KDIGO consensus, AKI is caused by a number of conditions and through various mechanisms.[12] The risk for AKI development is increased by exposure to factors that cause AKI and further increased by the presence of potential factors that increase susceptibility.[12] Susceptibilities outlined in the consensus include dehydration or volume depletion, advanced age, female sex, black race, chronic kidney disease (CKD), chronic disease including congestive heart failure, diabetes mellitus, cancer, and anemia.[12] Potential exposures include sepsis, critical

illness, circulatory shock, burns, trauma, cardiac surgery (especially cardiopulmonary bypass), major non-cardiac surgery including vascular surgery, nephrotoxic drugs, and radiocontrast agents.[12] The etiology of AKI in AAA repair is thought to be multifactorial including changes in renal perfusion, nephrotoxic drugs, ischemia-reperfusion injury, contrast-induced nephropathy, renal micro-embolization, acute tubular necrosis, hypovolemia and inflammatory and neuroendocrine stress response to surgery.[15–17]

2.3 Postoperative AKI among AAA repair patients

Acute kidney injury development in the postoperative setting is associated with significant morbidity, mortality, length of hospitalization and hospital costs.[12,18–22] Patients at increased risk for AKI after AAA repair are those who have pre-existing chronic kidney disease, hypertension, diabetes mellitus and who are older.[11,16,23–32] A retrospective cohort of 169 open elective transperitoneal juxtarenal AAA repair patients analyzing predictors for postoperative renal dysfunction determined technical factors including renal ischemia time, aortic clamp position and left renal vein division to be the strongest predictors.[33] The incidence of AKI in AAA repair is significantly higher in open repair patients compared with EVAR in a systematic review of short-term AAA results.[34] Castagno et al. performed a retrospective cohort of 146 infrarenal AAA repair patients that found similar effects with a significant increase in AKI among open repair patients compared with EVAR.[35] Another retrospective cohort of 6516 patients by Wald et al. found EVAR was associated with lower odds of AKI (OR 0.4, 95% CI 0.3-0.5) and AKI requiring dialysis (OR 0.3, 95% CI 0.2-0.6).[36] This is in contrast with another systematic review which found no difference between open and EVAR and postoperative AKI incidence.[9] A critical review of the epidemiology of AKI in vascular surgery patients reported incidences of

AKI in EVAR patients between 5.5% and 18%; and incidences of AKI up to 26% following open repair of an infrarenal AAA.[11] These incidences were both increased in the presence of significant clinical or surgical complexity.[11] EVAR requiring branched or fenestrated devices or requiring a snorkel or chimney surgical approach increased postoperative AKI incidence to 28% and 32% respectively.[11] Open repair patients requiring repair of a juxtarenal or suprarenal aneurysm increased postoperative AKI incidence to 47% and 68% respectively compared with infrarenal aneursyms.[11] In a systematic review, postoperative renal impairment among AAA repair patients was associated with increased mortality risk (HR 1.5, 95% CI, 1.4-1.7).[37] Increased mortality is not the only complication of postoperative AKI among the vascular patient as other morbidities and hospital costs are also associated with this outcome. Patients who develop postoperative AKI also have higher rates of cardiovascular events including myocardial infarction, infection, coagulopathy, and long-term risk of end-stage renal disease (ESRD). [11] It was demonstrated in a retrospective study that patients with postoperative AKI had hospital costs of $42 600 compared with patients that did not develop AKI and had hospital costs of $26 700.[38] As a consequence of postoperative AKI, 0.5% to 2% of elective AAA repair patients receive hemodialysis which is associated with in-hospital mortality of 25% to 66% of patients.[39] AKI has a significant impact on a patient's outcomes following AAA repair, and identifying potential strategies to prevent AKI would be beneficial. We examined two potential modifiable perioperative factors during AAA repair; ACE inhibitor and/or ARB use immediately preoperatively, and the impact of intraoperative hypotension and its management on the incidence of AKI after AAA repair.

2.4 ACE inhibitors and/or ARBs and AKI

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptors blockers (ARB) are anti-hypertensive drugs used to treat high blood pressure (hypertension) to reduce the long term risk of cardiovascular morbidity and mortality.[40] These drugs exert their effects by inhibiting the renin-angiotensin-aldosterone system (RAAS) .[40] RAAS inhibitors are the most prescribed drugs within this class, and the most common and relevant are ACE inhibitors and ARBs.[40] ACE/ARBs systemic effect on angiotensin II contributes to the development of intraoperative hypotension and to AKI through systemic hypotension and inhibition of efferent renal arteriolar vasoconstriction.[41]

There is conflicting evidence regarding the use of these drugs preoperatively among patients undergoing major surgery, some studies suggest discontinuing ACE/ARBs preoperatively while others found a reno-protective effect associated with their use.[11,12,41–51] In the vascular surgery setting, a number of cohort studies have suggested holding ACE/ARBs on the day of surgery/in the immediate preoperative setting.[11,46,52] In the EVAR setting, preoperative ARB use was significantly associated with postoperative AKI in a multivariable analysis of 212 patients who underwent AAA repair between January 2009 and October 2016 (OR 4.1, 95% CI 1.4 – 12.1).[53] In a separate study, Pisimisis et al. found a trend towards an association between ACE and AKI (P = 0.07) among 208 EVAR patients in a retrospective cohort.[46] In another retrospective cohort study of 268 patients, specifically looking at AAA repair, they determined there to be insufficient evidence to make any conclusions regarding the use of ACE/ARBs in the preoperative setting of open and EVAR infrarenal AAA repair using propensity score matching.[22]

In the cardiac surgery setting, a meta-analysis of ACE/ARB use in the preoperative setting was conducted that identified a significant increase in odds of AKI and mortality among ACE/ARB users.[54] A narrative review of the effects of the combined use of ACE inhibitors and ARBs showed an increased risk of AKI.[49] A prospective cohort study of 1287 cardiac surgery patients examined the association between the preoperative use of ACE/ARBs and AKI, assessing both structural (defined based on peak postoperative levels of urinary biomarkers) and functional effects (defined based on changes in preoperative and postoperative serum creatinine). It determined a significant association between ACE/ARBs and structural AKI.[41] A retrospective cohort study of 1287 patients found a reno-protective effect due to preoperative ACE/ARB use for aging cardiac surgery patients, therefore completely contradicting the results above.[48]

Among noncardiac surgery patients, a systematic review concluded using low level evidence that ACE/ARBs should be held in the perioperative period to limit hypotension.[51] Some studies, reviews and meta-analyses found a protective effect for continuing ACE/ARBs in the preoperative setting against postoperative AKI.[42,45,55]

The consensus among this conflicting literature is that currently there is insufficient high-quality evidence to make a strong recommendation as to whether or not ACE/ARBs should be held immediately before surgery or given the morning of surgery.[42–45,47,50,56] Similarly, the KDIGO consensus has stated in its recommendations that there is not enough evidence to recommend discontinuation.[12]

A major discrepancy between systematic reviews and meta-analyses is that the pooled studies have different time points of ACE/ARB use, some defined pre-operative use of ACE/ARBs as within 120 days, some defined it as within 2 weeks and some defined it as within 24 hours.

These time points analyze very different ideas: prolonged use of ACE/ARB vs. immediate pre-operative use ask different questions and use different mechanisms when considering long-term use vs. anti-hypertensive mechanisms during the intraoperative time period. The ultimate consensus for all studies is the need for further analysis of the association between these drugs and AKI, most calling for multi-centre randomized controlled trials using appropriate definitions of AKI and predefined time points of ACE/ARB administration and dosage. We utilized the data from a RCT of curcumin versus placebo which was prospectively collected to try and add further evidence to this question.

2.5 Intraoperative hypotension and AKI

Intraoperative hypotension is a common occurrence during surgery and has been shown to be statistically associated with adverse outcomes.[11,57,58] It can occur as a result of a number of reasons including general anesthesia, blood loss, or pre-operative or intraoperative use of different drugs including ACE/ARBs.[51,57] There is currently no widely accepted definition of intraoperative hypotension; different studies define this complication using different measures such as systolic blood pressure (SBP), mean arterial pressure (MAP), and central venous pressure (CVP), among others.[57,59,60] Despite varying definitions, an association between intraoperative hypotension and mortality and AKI has been determined in a number of studies across different types of surgery. [16,59–66] A systematic review of this topic was conducted to determine if and to what extent intraoperative hypotension disrupts organ perfusion and damages organs among non-cardiac surgery patients.[57] They determined an increased risk for AKI and mortality at MAP < 80 mmHg for longer than 10 minutes and increased further with increased duration or with lower MAP.[57] They call for future prospective studies looking at specific patient

populations and a clear definition for hypotension and outcomes, for example using KDIGO to define AKI.[57] The difference between 30 seconds of a MAP of 40 mmHg and 5 minutes of a MAP of 50mmHg is important. The former is well tolerated for almost all patients while the latter would be harmful. The intersection between severity of hypotension and duration of hypotension is an important consideration within intraoperative hypotension research.

Among patients undergoing AAA repair, a number of studies have examined the association between hypotension and AKI or mortality. Tallgren et al. determined a statistically significant association between intraoperative hypotension and AKI in a multivariable analysis of 69 AAA repair patients in a prospective cohort study (OR 8.5, 95% CI 1.8-39.4, $P = 0.006$).[16] Brinkman et al. determined that the increased duration and prominence of intraoperative hypotension, defined as MAP 65 mmHg, to be the most significant intraoperative risk factor for the development of postoperative AKI among 40 open AAA repair patients in a pilot prospective observational trial.[64] In a retrospective cohort of 71 AAA repair patients of both open and endovascular repair, Yue et al. identified intraoperative hypotension as a significant risk factor for AKI (OR=6.0, 95% CI 1.2-30.7) according to the RIFLE criteria.[67] Intraoperative hypotension is also significantly associated with significant consequences including 30 day mortality(OR 6.6, 95% CI 0.7–61.1, $P = 0.06$) among a retrospective cohort study of 450 open AAA repair patients.[68] Van Waes et al. performed a retrospective cohort study of 890 vascular surgery patients and determined a significant association between myocardial injury and intraoperative hypotension (RR 1.8, 99% CI 1.2 - 2.6, $P < 0.001$).[66] They concluded future studies should include the different treatments for intraoperative hypotension to understand their influence on the association between intraoperative hypotension and myocardial injury for evidence-based decisions regarding proper care.[66]

Noncardiac surgery studies were conducted to analyze the association between intraoperative hypotension and AKI or mortality and they all determined a significant increased association.[59–61,63,65,69,70] Walsh et al. determined hypotension, defined as MAP <55 mmHg was also associated with postoperative AKI, even for short durations among 33 330 noncardiac surgery patients in a retrospective cohort study.[60] Patients with the longest duration of MAP <55mmHg defined as greater than 20 minutes had a 1.5 fold increase in risk of AKI or myocardial injury and 2.0 fold increase in risk for cardiac complications.[60] Vernooij et al. performed a retrospective cohort study of 10 432 noncardiac surgery patients to analyze how different methods for defining intraoperative hypotension yielded different levels of significance with the outcomes of postoperative myocardial infarction and AKI.[59] They looked at 8 different methods for defining hypotension including: MAP <50mmHg, MAP <60mmHg, SBP<70mmHg, SBP<90mmHg, 20% and 40% decrease in SBP from baseline, and 20% and 40% decrease in MAP from baseline. They determined that none of the effect sizes using one of these measures was any stronger than the others and that future studies should look at SBP compared with MAP for defining intraoperative hypotension using different cutoffs and durations. They encourage use of more stringent definitions to determine the most significant outcomes.[59] In terms of AKI, they determined use of MAP < 50 mmHg to yield the most significant odds ratios using definitions of: presence of intraoperative hypotension, mean duration of hypotension, absolute decrease in blood pressure and mean episode area under threshold as models for the relationship between intraoperative hypotension and AKI (standardized OR 1.2 99%CI 1.0-1.4).[59] Sun et al. determined a significant association between intraoperative hypotension, defined using MAP < 55mmHg, and postoperative AKI in a retrospective cohort study of 5127 noncardiac surgery patients.[63] They found patients with a MAP <55mmHg had 2.3 times the odds (95% CI 1.4–4.1)

of AKI if the duration of hypotension was between 11 and 20 minutes and 3.5 times the odds (95% CI 1.5–8.3) of AKI if the duration of hypotension was greater than 20 minutes compared with patients who had 0 minutes of hypotension.[63] They call for RCTs analyzing interventions to treat or prevent intraoperative hypotension and its associated adverse outcomes.[63] The American College of Surgeons – National Surgical Quality Improvement Program used prospectively collected data on 152 244 general surgery operations in the United States in 2005−2006 which found among patients at high risk for AKI, periods of MAP <60 mmHg were more common among patients who developed AKI than among those who did not.[70] Cohort studies among noncardiac surgery patients also determined a significant association between intraoperative hypotension and mortality in both prospective and retrospective settings (P<0.05).[61,65] Monk et al. in a prospective cohort study of 1064 non cardiac surgery patients found patients with intraoperative hypotension had 1.04 times the risk per minute of mortality within 1 year of surgery compared with patients with normal intraoperative blood pressure(P=0.01).[61] Sabate et al. in a prospective multicenter observational cohort study of noncardiac surgery patients found a significant association with postoperative major adverse cardiac and cerebrovascular events(P<0.0001).[69]

An association between pre-operative ACE inhibitors and/or ARB use and intraoperative hypotension has been proposed in a RCT by Bertrand et al. and a retrospective cohort study by Brabant et al. in the AAA repair setting.[52,62] Bertrand et al. analyzed 37 patients undergoing major vascular surgery including AAA repair, carotid endarterectomy, and infraguinal revascularization.[52] Brabant et al. analyzed 84 hypertensive patients scheduled for vascular surgery.[62] They determined a statistically significant association and suggested holding ACE/ARBs in the immediate preoperative setting to limit potential for intraoperative

hypotension and its associated adverse outcomes(P<0.05).[52,62] Studies involving noncardiac patients determined a similar association and identified intraoperative hypotension as a significant risk factor for AKI among hospitalized patients (P=0.001).[51,71] These results are questioned in a systematic review which found a protective effect of ACE/ARBs in the perioperative setting.[47] Further research is required to confirm or deny these findings.

Different measures and cutoffs are often used to define intraoperative hypotension and one has not been proven to be definitively better than any of the others. The duration of intraoperative hypotension is also an important consideration. Although intraoperative hypotension and its association with AKI has been extensively studied, different methods to treat intraoperative hypotension and its effects on AKI have not been clearly elucidated. Our data allow us to evaluate whether treating intraoperative hypotension primarily with inotropes/vasopressors or fluid has an added effect on the incidence of AKI after AAA repair.

2.6 Preventive strategies for AKI among AAA repair patients

At this time, a systematic review or meta-analysis has not been conducted to identify or evaluate potential preventive measures for AKI among AAA repair patients. A number of cohort studies have been conducted to evaluate interventions or preventive strategies in this setting including Pisimisis et al. which states that identification of modifiable perioperative risk factors can be used to determine strategies to improve renal outcomes among AAA repair patients. They identified contrast volume and ACE inhibitors as possible areas for improvement in a retrospective cohort study of 208 EVAR patients.[72] Tallgren et al. identified hypotension and low cardiac output as risk factors that could be targeted for preventive strategies among 69 elective AAA repair patients in a prospective cohort study.[16] Mannitol has been suggested to be a

preventive intervention of interest among AAA repair patients in a number of cohort and RCT studies.[33,73,74] Zabrocki et al. suggest endovascular repair to be considered a preventive strategy for AKI and call for a large RCT to assess EVAR vs open repair and a bundle of measures and their effect on reducing AKI following their analysis of 268 AAA repair patients in a retrospective cohort.[22] Contrast agents have been identified as risk factors for AKI and different methods or timing of administration have been suggested[11,58,75]

A review by Saratzis et al. describing AKI after EVAR describes the pathophysiology of the outcome and describes various preventive strategies for AKI.[76] They included hydration, ischemic preconditioning, regional anesthesia and pharmacological agents as preventive strategies with a low level of evidence, however, this was not a systematic review and it does not evaluate patients with open repair.[76] A systematic review by Zacharias et al. analyzed AKI and mortality in the perioperative period of major surgery patients, however, they did not include AAA repair patients.[56] Systematic reviews involving AKI as a postoperative outcome of interest have proven difficult due to a lack of similar definitions.[77] A systematic review analyzing preventive strategies or interventions for AKI among cardiac surgery patients has been conducted to consolidate the information on this at risk population and a number of targets were identified for further study.[78] A systematic review in the AAA repair setting would be of interest to determine preventive strategies or interventions to reduce AKI among this at-risk group.

2.7 References

1. Kuivaniemi H, Ryer EJ, Elmore JR, Tromp G. Understanding the pathogenesis of abdominal aortic aneurysms. Expert Rev Cardiovasc Ther. 2015;13(9):975–87.

2. Kapila V, Jetty P, Wooster D, Vucemilo V, Dubois L. 2018 Screening for abdominal

aortic aneurysms in Canada: Review and position statement from the Canadian Society of Vascular Surgery [Internet]. Canadian Society for Vascular Surgery. 2018. Available from: https://vascular.ca/resources/Documents/Clinical-Guidelines/FINAL-2018-CSVS-Screening-Recommendations.pdf

3. Altobelli E, Rapacchietta L, Profeta VF, Fagnano R. Risk factors for abdominal aortic aneurysm in population-based studies: A systematic review and meta-analysis. Int J Environ Res Public Health. 2018;15(12).

4. Paravastu SCV, Jayarajasingam R, Cottam R, Palfreyman SJ, Michaels JA, Thomas SM. Endovascular repair of abdominal aortic aneurysms. Cochrane Database Syst Rev. 2014;(1):1–48.

5. Takagi H, Ando T, Umemoto T. Worse late-phase survival after elective endovascular than open surgical repair for intact abdominal aortic aneurysm. Int J Cardiol. 2017;236:427–31.

6. Powell JT, Sweeting MJ, Ulug P, Blankensteijn JD, Lederle FA, Becquemin JP, et al. Meta-analysis of individual-patient data from EVAR-1, DREAM, OVER and ACE trials comparing outcomes of endovascular or open repair for abdominal aortic aneurysm over 5 years. Br J Surg. 2017;104(3):166–78.

7. Adriaensen MEAPM, Bosch JL, Halpern EF, Myriam Hunink MG, Gazelle GS. Elective Endovascular versus open surgical repair of abdominal oortic aneurysms: Systematic review of short-term results. Radiology. 2007;224(3):739–47.

8. Patel R, Sweeting MJ, Powell JT, Greenhalgh RM. Endovascular versus open repair of abdominal aortic aneurysm in 15-years' follow-up of the UK endovascular aneurysm repair trial 1 (EVAR trial 1): a randomised controlled trial. Lancet. 2016;388(10058):2366–74.

9. Stather PW, Sidloff D, Dattani N, Choke E, Bown MJ, Sayers RD. Systematic review and meta-analysis of the early and late outcomes of open and endovascular repair of abdominal aortic aneurysm. Br J Surg. 2013;100(7):863–72.

10. Li B, Khan S, Salata K, Hussain MA, de Mestral C, Greco E, et al. A systematic review and meta-analysis of the long-term outcomes of endovascular versus open repair of abdominal aortic aneurysm. J Vasc Surg. 2019;

11. Hobson C, Lysak N, Huber M, Scali S, Bihorac A. Epidemiology, outcomes, and management of acute kidney injury in the vascular surgery patient. J Vasc Surg. 2018;68(3):916–28.

12. KDIGO. Clinical practice guideline for acute kidney injury (AKI). Kidney Int Suppl. 2012;2(1):4.

13. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure: definition, outcome measures, animal models, fluid therapy and information technology needs. Crit Care. 2004;8(4):r204-12.

14. Mehta RL, Kellum JA, Shah S V., Molitoris BA, Ronco C, Warnock DG, et al. Acute kidney injury network: report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11(2):1–8.

15. Minami K, Sugiyama Y, Iida H. A retrospective observational cohort study investigating the association between acute kidney injury and all-cause mortality among patients undergoing endovascular repair of abdominal aortic aneurysms. J Anesth. 2017;31(5):686–91.

16. Tallgren M, Niemi T, Poyhia R, Raininko E, Railo M, Salmenpera M, et al. Acute renal injury and dysfunction following elective abdominal aortic surgery. Eur J Vasc Endovasc Surg. 2007;33(5):550–5.

17. Saratzis A, Melas N, Mahmood A, Sarafidis P. Incidence of acute kidney injury (AKI) after endovascular abdominal aortic aneurysm repair (EVAR) and impact on outcome. Eur J Vasc Endovasc Surg. 2015;49(5):534–40.

18. Saratzis A, Shakespeare J, Jones O, Bown MJ, Mahmood A, Imray CHE. Pre-operative functional cardiovascular reserve is associated with acute kidney injury after intervention. Eur J Vasc Endovasc Surg. 2017;53(5):717–24.

19. Tang Y, Chen J, Huang K, Luo D, Liang P, Feng M, et al. The incidence, risk factors and in-hospital mortality of acute kidney injury in patients after abdominal aortic aneurysm repair surgery. BMC Nephrol. 2017;18(1):184.

20. Boyle JR. Preventing EVAR associated acute kidney injury: the optimal strategy remains elusive. Eur J Vasc Endovasc Surg. 2018;55(5):657.

21. Becquemin JP, Chemla E, Chatellier G, Allaire E, Mellière D, Desgranges P. Perioperative factors influencing the outcome of elective abdominal aorta aneurysm repair. Eur J Vasc Endovasc Surg. 2000;20(1):84–9.

22. Zabrocki L, Marquardt F, Albrecht K, Herget-Rosenthal S. Acute kidney injury after abdominal aortic aneurysm repair: current epidemiology and potential prevention. Int Urol Nephrol. 2018;50(2):331–7.

23. Chiesa R, Marone EM, Brioschi C, Frigerio S, Tshomba Y, Melissano G. Open repair of pararenal aortic aneurysms: operative management, early results, and risk factor analysis. Ann Vasc Surg. 2006;20(6):739–46.

24. Luft FC, Hamburger RJ, Dyer JK, Szwed JJ, Kleit SA. Acute renal failure following operation for aortic aneurysm. Surg Gynecol Obstet. 1975;141(3):374–8.

25. Ellenberger C, Schweizer A, Diaper J, Kalangos A, Murith N, Katchatourian G, et al. Incidence, risk factors and prognosis of changes in serum creatinine early after aortic abdominal surgery. Intensive Care Med. 2006;32:1808-1816.

26. Sarac TP, Clair DG, Hertzer NR, Greenberg RK, Krajewski LP, O'Hara PJ, et al. Contemporary results of juxtarenal aneurysm repair. J Vasc Surg. 2002;36(6):1104–11.

27. Jean-Claude JM, Reilly LM, Stoney RJ, Messina LM. Pararenal aortic aneurysms: The future of open aortic aneurysm repair. J Vasc Surg. 1999;29(5):902–12.

28. Johnston KW. Multicenter prospective study of nonruptured abdominal aortic aneurysm. Part II. Variables predicting morbidity and mortality. J Vasc Surg. 1989;9(3):437–47.

29. Hertzer NR, Mascha EJ, Karafa MT, O'Hara PJ, Krajewski LP, Beven EG. Open infrarenal abdominal aortic aneurysm repair: The Cleveland Clinic experience from 1989 to 1998. J Vasc Surg. 2002;35(6):1145–54.

30. Alsac JM, Zarins CK, Heikkinen MA, Karwowski J, Arko FR, Desgranges P, et al. The impact of aortic endografts on renal function. J Vasc Surg. 2005;41(6):926–30.

31. Powell RJ, Roddy SP, Meier GH, Gusberg RJ, Conte MS, Sumpio BE. Effect of renal insufficiency on outcome following infrarenal aortic surgery. Am J Surg. 1997;174(2):126–30.

32. Cohen JR, Mannick JA, Couch NP. Abdominal aortic aneurysm repair in patients with preoperative renal failure. J Vasc Surg. 1986;3(6):867–70.

33. Dubois L, Durant C, Harrington DM, Forbes TL, Derose G, Harris JR. Technical factors are strongest predictors of postoperative renal dysfunction after open transperitoneal juxtarenal abdominal aortic aneurysm repair. J Vasc Surg. 2013;57(3):648–54.

34. Diehl JT, Cali RF, Hertzer NR, Beven EG. Complications of abdominal aortic reconstruction. An analysis of perioperative risk factors in 557 patients. Surv Anesthesiol. 1983;27(1):49–56.

35. Castagno C, Varetto G, Quaglino S, Frola E, Scozzari G, Bert F, et al. Acute kidney injury after open and endovascular elective repair for infrarenal abdominal aortic aneurysms. J Vasc Surg. 2016;64(4):928+.

36. Wald R, Waikar SS, Liangos O, Pereira BJG, Chertow GM, Jaber BL. Acute renal failure after endovascular vs open repair of abdominal aortic aneurysm. J Vasc Surg. 2006;43(3):466.

37. Khashram M, Williman JA, Hider PN, Jones GT, Roake JA. Systematic review and meta-analysis of factors influencing survival following abdominal aortic aneurysm repair. Eur J Vasc Endovasc Surg. 2016;51(2):203–15.

38. Hobson C, Ozrazgat-Baslanti T, Kuxhausen A, Thottakkara P, Efron PA, Moore FA, et al.

Cost and mortality associated with postoperative acute kidney injury. Ann Surg. 2015;261(6):1207–14.

39. Wald R, Waikar SS, Liangos O, Pereira BJG, Chertow GM, Jaber BL. Acute renal failure after endovascular vs open repair of abdominal aortic aneurysm. J Vasc Surg. 2006;43(3):466.

40. Van Vark LC, Bertrand M, Akkerhuis KM, Brugts JJ, Fox K, Mourad JJ, et al. Angiotensin-converting enzyme inhibitors reduce mortality in hypertension: A meta-analysis of randomized clinical trials of renin-angiotensin-aldosterone system inhibitors involving 158 998 patients. Eur Heart J. 2012;33(16):2088–97.

41. Coca SG, Garg AX, Swaminathan M, Garwood S, Hong K, Thiessen-Philbrook H, et al. Preoperative angiotensin-converting enzyme inhibitors and angiotensin receptor blocker use and acute kidney injury in patients undergoing cardiac surgery. Nephrol Dial Transplant. 2013;28(11):2787–99.

42. Shah M, Jain AK, Brunelli SM, Coca SG, Devereaux PJ, James MT, et al. Association between angiotensin converting enzyme inhibitor or angiotensin receptor blocker use prior to major elective surgery and the risk of acute dialysis. BMC Nephrol. 2014;15(1):1–9.

43. Drake TM, Cheung LK, Gaba F, Glasbey J, Griffiths N, Helliwell RJ, et al. Association between peri-operative angiotensin-converting enzyme inhibitors and angiotensin-2 receptor blockers and acute kidney injury in major elective non-cardiac surgery: a multicentre, prospective cohort study. Anaesthesia. 2018;73(10):1214–22.

44. Tagawa M, Ogata A, Hamano T. Pre- and/or intra-operative prescription of diuretics, but not renin-angiotensin-system inhibitors, is significantly associated with acute kidney injury after non-cardiac surgery: a retrospective cohort study. PLoS One. 2015;10(7):e0132507.

45. Cheungpasitporn W, Thongprayoon C, Srivali N, O'Corragain OA, Edmonds PJ, Ungprasert P, et al. Preoperative renin-angiotensin system inhibitors use linked to reduced acute kidney injury: a systematic review and meta-analysis. Nephrol Dial Transplant.

2015;30(6):978–88.

46. Pisimisis GT, Bechara CF, Barshes NR, Lin PH, Lai WS, Kougias P. Risk factors and impact of proximal fixation on acute and chronic renal dysfunction after endovascular aortic aneurysm repair using glomerular filtration rate criteria. Ann Vasc Surg. 2013;27(1):16–22.

47. Ling Q, Gu Y, Chen J, Chen Y, Shi Y, Zhao G, et al. Consequences of continuing renin angiotensin aldosterone system antagonists in the preoperative period: a systematic review and meta-analysis. BMC Anesthesiol. 2018;18(1):26.

48. Barodka V, Silvestry S, Zhao N, Jiao X, Whellan DJ, Diehl J, et al. Preoperative renin-angiotensin system inhibitors protect renal function in aging patients undergoing cardiac surgery. J Surg Res. 2011;167(2):e63–9.

49. Chen SS, Seliger SL, Fried LF. Complete inhibition of the renin-angiotensin-aldosterone system; where do we stand? Curr Opin Nephrol Hypertens. 2014;23(5):449–55.

50. Zhou L, Duan S. Effects of angiotensin converting enzyme inhibitors and angiotensin receptor blockers in contrast-induced nephropathy. Kidney Blood Press Res. 2013;38(2–3):165–71.

51. Vaquero Roncero LM, Sánchez Poveda D, Valdunciel García JJ, Sánchez Barrado ME, Calvo Vecino JM. Perioperative use of angiotensin-converting-enzyme inhibitors and angiotensin receptor antagonists. J Clin Anesth. 2017;40:91–8.

52. Bertrand M, Godet G, Meersschaert K, Salcedo E, Coriat P. Should the angiotensin II antagonists be discontinued. Anesth Analg. 2001;92:26–30.

53. Statius van Eps RG, Nemeth B, Mairuhu RTA, Wever JJ, Veger HTC, van Overhagen H, et al. Determinants of acute kidney injury and renal function decline after endovascular abdominal aortic aneurysm repair. Eur J Vasc Endovasc Surg. 2017;54(6):712–20.

54. Yacoub R, Patel N, Lohr JW, Rajagopalan S, Nader N, Arora P. Acute kidney injury and death associated with renin angiotensin system blockade in cardiothoracic surgery: A

meta-analysis of observational studies. Am J Kidney Dis. 2013;62(6):1077–86.

55. Peng F, Su J, Lin J, Niu W. Impact of renin-angiotensin-aldosterone system-blocking agents on the risk of contrast-induced acute kidney injury: a prospective study and meta-analysis. J Cardiovasc Pharmacol. 2015;65(3):262–8.

56. Zacharias M, Mugawar M, Herbison GP, Walker RJ, Hovhannisyan K, Sivalingam P, et al. Interventions for protecting renal function in the perioperative period. Cochrane Database Syst Rev. 2013;(9).

57. Wesselink EM, Kappen TH, Torn HM, Slooter AJC, van Klei WA. Intraoperative hypotension and the risk of postoperative adverse outcomes: a systematic review. Br J Anaesth. 2018;121(4):706–21.

58. Goren O, Matot I. Perioperative acute kidney injury. Br J Anaesth. 2015;115(2, SI):3–14.

59. Vernooij LM, van Klei WA, Machina M, Pasma W, Beattie WS, Peelen LM. Different methods of modelling intraoperative hypotension and their association with postoperative complications in patients undergoing non-cardiac surgery. Br J Anaesth. 2018;120(5):1080–9.

60. Walsh M, Devereaux PJ, Garg AX, Kurz A, Turan A, Rodseth RN et al. Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery. Anesthesiology. 2013;119(3):507–15.

61. Monk TG, Saini V, Weldon BC, Sigl JC. Anesthetic management and one-year mortality after noncardiac surgery. Anesth Analg. 2005;100(1):4–10.

62. Brabant SM, Bertrand M, Eyraud D, Darmon P-L, Coriat P. The hemodynamic effects of anesthetic induction in vascular surgical patients chronically rreated with angiotensin II receptor antagonists. Anesth Analg. 1999;89(6):1388.

63. Sun LY, Wijeysundera DN, Tait GA, Beattie WS. Association of intraoperative hypotension with acute kidney injury after elective non-cardiac surgery. Anesthesiology. 2015;123(3):515–23.

64. Brinkman R, HayGlass KT, Mutch WAC, Funk DJ. Acute kidney injury in patients undergoing open abdominal aortic aneurysm repair: A pilot observational trial. J Cardiothorac Vasc Anesth. 2015;29(5):1212–9.

65. Bijker JB, van Klei WA, Vergouwe Y, Eleveld DJ, van Wolfswinkel L, Moons KGM, et al. Intraoperative hypotension and 1-year mortality after noncardiac surgery. Anesthesiology. 2009;111(6):1217–26.

66. van Waes JAR, van Klei WA, Wijeysundera DN, van Wolfswinkel L, Lindsay TF, Beattie WS. Association between intraoperative hypotension and myocardial injury after vascular surgery. Anesthesiology. 2015;124(1):35–44.

67. Yue J-N, Luo Z, Guo D-Q, Xu X, Chen B, Jiang J-H, et al. Evaluation of acute kidney injury as defined by the risk, injury, failure, loss, and end-stage criteria in critically ill patients undergoing abdominal aortic aneurysm repair. Chin Med J (Engl). 2013;126(3):431–6.

68. Davidovic LB, Maksic M, Koncar I, Ilic N, Dragas M, Fatic N, et al. Open repair of AAA in a high volume center. World J Surg. 2017;41(3):884–91.

69. Sabaté S, Mases A, Guilera N, Canet J, Castillo J, Orrego C, et al. Incidence and predictors of major perioperative adverse cardiac and cerebrovascular events in non-cardiac surgery. Br J Anaesth. 2011;107(6):879–90.

70. Kheterpal S, Tremper KK, Heung M, Rosenberg AL, Englesbe M, Shanks AM, et al. Development and validation of an acute kidney injury risk index for patients undergoing general surgery: Results from a national data set. Anesthesiology. 2009;110(3):505–15.

71. Alabdan N, Gosmanova EO, Tran NQT, Oliphant CS, Pan H, Broyles JE, et al. Acute kidney injury in patients continued on renin-angiotensin system blockers during hospitalization. Am J Med Sci. 2017;353(2):172–7.

72. Pisimisis G, Kantor B, Khoynezhad A, Lahr BD, Bailey KR, Kruse MJ, et al. Incidence and risk factors of renal dysfunction after thoracic endovascular aortic repair. J Vasc Surg. 2009;49:36S.

73. Kalimeris K, Nikolakopoulos N, Riga M, Christodoulaki K, Moulakakis KG, Dima C, et al. Mannitol and renal dysfunction after endovascular aortic aneurysm repair procedures: A randomized trial. J Cardiothorac Vasc Anesth. 2014;28(4):966–71.

74. Mazze RI, Barry KG. Prevention of functional renal failure during anesthesia and surgery by sustained hydration and mannitol infusion. Anesth Analg. 1967;46(1):61–8.

75. Macedo E, Castro I, Yu L, Abdulkader RRC, Vieira Jr. JM. Impact of mild acute kidney injury (AKI) on outcome after open repair of aortic aneurysms. Ren Fail. 2008;30(3):287–96.

76. Saratzis AN, Goodyear S, Sur H, Saedon M, Imray C, Mahmood A. Acute kidney injury after endovascular repair of abdominal aortic aneurysm. J Endovasc Ther. 2013;20(3):315–30.

77. O'Connor ME, Kirwan CJ, Pearse RM, Prowle JR. Incidence and associations of acute kidney injury after major abdominal surgery. Intensive Care Med. 2016;42(4):521–30.

78. Park M, Coca SG, Nigwekar SU, Garg AX, Garwood S, Parikh CR. Prevention and treatment of acute kidney injury in patients undergoing cardiac surgery: A systematic review. Am J Nephrol. 2010;31(5):408–18.

Chapter 3

3 Exploring target areas for development of preventive strategies for acute kidney injury in patients undergoing abdominal aortic aneurysm repair

To identify target areas for development of preventive strategies for acute kidney injury following abdominal aortic aneurysm repair, we performed a secondary data analysis of the curcumin randomized controlled trial. In this secondary data analysis, we assessed the association between angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker use within 24 hours of repair with postoperative AKI to examine the proposed effect of these anti-hypertensive drugs in the preoperative period. We also assessed the association between intraoperative hypotension and its associated treatments with postoperative AKI. This chapter consists of four sections including a brief introduction, description of methods, an in-depth report of results followed by a discussion.

3.1 Introduction

An abdominal aortic aneurysm (AAA) is a widening or ballooning of the aorta in the abdomen and is associated with high morbidity and mortality.[1–4] It can be repaired surgically using an open or endovascular procedure, however, postoperative acute kidney injury (AKI) remains a major complication associated with poor outcomes.[1–8] Patients with AKI are at increased risk of morbidity, mortality and length of hospitalization.[2–8] Identifying target areas for development of preventive strategies or treatment options may improve the outcomes of patients following AAA repair. Risk factors for AKI among AAA repair include pre-existing chronic kidney disease, advanced age, diabetes, hypertension, congestive heart failure, prolonged renal ischemia time,

transfusion, open repair, nephrotoxic medications, atheroembolizaition to the kidney, intraoperative hypotension, preoperative use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB), and statins, among others.[1–7,9–12]

ACE inhibitors and ARBs are antihypertensive medications which exert their effects by inhibiting the renin-angiotensin system (RAS). They have been shown to increase the risk of postoperative AKI in a number of patient settings including after abdominal aortic aneurysm repair. This association has been largely studied in the cardiac surgery setting and has demonstrated conflicting results for a positive or negative effect on risk of postoperative AKI.[13–15] The majority of studies indicate that preoperative use of RAS inhibitors increases the risk for postoperative AKI among major elective surgery patients including cardiac and vascular procedures.[6,9,11,14–27] However, among non-cardiac surgery studies, preoperative use of ACE inhibitors and/or ARBs have failed to show a significant increase in risk for postoperative AKI.[17,28] Among a retrospective cohort of 212 endovascular repair patients, ARBs were shown to be significantly associated with postoperative AKI (OR 4.1 95% CI: 1.4-12.1).[11] In another retrospective cohort study of 208 patients undergoing EVAR, ACE inhibitors showed a trend to be predictors for AKI (P=0.07).[29] There are obvious discrepancies in the literature with different definitions of AKI in different patient settings, and it is clear that more studies are needed.

Intraoperative hypotension, using varying definitions, has been widely associated with AKI and postoperative mortality across varying clinical settings, presumably due to its limiting effect on organ perfusion. The definition and consistent classification of intraoperative hypotension has not been clearly established in the literature.[30,31] For the purpose of this study, intraoperative hypotension was defined using systolic blood pressure (SBP) with a threshold of <100mmHg, which has been previously used in a number of other studies.[30,31] Hypotension is associated with

AKI and mortality in non-cardiac and vascular surgery patients.[2,20,30–45] Intraoperative treatment of hypotension include fluids, blood transfusion, inotropes or vasopressors or no treatment at all. The optimal treatment has not been established. Van Waes et al.[36] performed a retrospective cohort of 890 vascular surgery patients and analyzed the association between intraoperative hypotension and myocardial injury. They urge future studies to investigate the association between intraoperative hypotension and its treatments and the interactions associated with these factors and postoperative outcomes including myocardial injury.[36] Sun et al. performed a retrospective cohort study of 5127 patients undergoing noncardiac surgery and they concluded that future research is needed to consider the treatments of intraoperative hypotension when analyzing outcomes including acute kidney injury.[38] These suggestions to analyze intraoperative hypotension treatments were considered in the design of this analysis.

We conducted this secondary data analysis of the curcumin RCT in patients undergoing AAA repair to understand the association between the use of ACE inhibitors/ARBs immediately prior to surgery with the risk of AKI after AAA repair; and to explore the association between intraoperative hypotension and its method of treatment (inotropes/vasopressors, fluids or no treatment) with the risk of postoperative AKI.

3.2 Methods

3.2.1 Data Source and Sample

The curcumin trial[46] was a parallel-group, randomized, placebo-controlled trial of 606 patients from 10 centres across Canada who underwent an elective AAA repair between November 2011 and November 2014 in hopes of preventing perioperative complications. This is the largest RCT

to date on the topic of AKI prevention in AAA patients. The inclusion and exclusion criteria for patient recruitment to this RCT are included in Appendix A. Patients, health care providers and local research staff were blinded to treatment assignment. The trial was conducted to assess the effects of perioperative administration of curcumin on the primary outcome of postoperative inflammatory response and secondary outcomes including acute kidney injury, length of hospital stay, and a composite of clinical events. Curcumin is a herbal supplement derived from the turmeric plant and is believed to prevent ischemic reperfusion injury and toxin induced injury among animal studies and a previous human RCT. The study population included elective adult patients undergoing either open or endovascular AAA repair. From the overall data set, 5 patients were removed for the purpose of all analyses. Of the 5 patients removed, 4 patients were removed as they did not receive either open or EVAR rather they converted from the EVAR procedure to the open and the other patient was missing follow up data on AKI and all of their information was removed. This study's strengths included its size relative to comparable literature, the prospective nature of its data collection, and the adjudication of its outcomes.

3.2.2 ACE inhibitors and/or ARBs

ACE inhibitors and/or ARBs were defined as a dichotomous variable for the purpose of this study. Patients who received an ACE inhibitor and/or ARB in the 24 hours prior to repair were compared with patients who did not receive an ACE inhibitor and/or ARB or received an ACE inhibitor and/or ARB greater than 24 hours prior to repair. For the ACE inhibitor and/or ARB analysis, 2 additional patients were removed for missing values in the hypertension category.

3.2.3 Intraoperative hypotension: SBP < 100mmHg

Intraoperative hypotension was defined as a patient whose SBP dropped below 100mmHg during repair. The analysis was completed using a categorical variable defined according to the treatment of intraoperative hypotension. Patients were either treated with fluids or inotropes/vasopressors or received no treatment and were compared with patients who did not have intraoperative hypotension during repair (i.e. maintained SBP > 100mmHg). For the SBP <100mmHg analysis, 9 additional patients were removed for missing values in the SBP <100mmHg and hypertension categories.

3.2.4 AKI

The KDIGO criteria defines acute kidney injury as either: a 0.3mg/dL (or 26.5umol/L) increase in serum creatinine in the 48 hours following surgery from the pre-operative value, or a 50% increase in serum creatinine the 7 days following surgery from the preoperative value.[5,46] For the purpose of this analysis the primary study outcome, AKI, was represented using the 7 day criteria. AKI was reported as a dichotomous outcome (i.e. yes or no).

3.2.5 Covariates for Multivariable Analyses

The covariates adjusted for in the multivariable analyses were chosen *a priori* based on existing literature. Age, pre-existing chronic kidney disease, repair type performed, diabetes, hypertension, aneurysm size and intraoperative hypotension were adjusted for in the ACE/ARB analyses. Age, pre-existing chronic kidney disease, repair type performed, diabetes, hypertension, and aneurysm size were adjusted for in the intraoperative hypotension analyses. Adjusting for these variables is standard amongst studies of AAA repair patients as well as

cardiac and non-cardiac patient settings. Age is overwhelmingly adjusted for in AAA repair settings looking at AKI, as well as amongst a variety of other surgical settings.[6,7,10,11,13,14,17,19,23,31,32,47,48] Biological sex, hypertension, and diabetes are also controlled for very often.[6,7,10,11,13,14,17,19,23,28,31,32,38,47,49] Pre-operative kidney function is also commonly controlled for and pre-existing chronic kidney disease is considered to be one of the strongest predictors for AKI.[6,7,38,11,13,14,17,20,23,28,31] The size of the aneurysm is also commonly controlled for as well as the type of repair performed regarding the repair procedure.[10,11]Age, years and aneurysm size (diameter), mm were reported as continuous variables. Preexisting chronic kidney disease was reported as a dichotomous variable using the estimated glomerular filtration rate (eGFR): eGFR<60 mL/min/1.73m^2 vs eGFR>60 mL/min/1.73m^2. Repair type performed was reported as a dichotomous variable: endovascular repair or open repair. Diabetes (Type I and II) and hypertension (treated) were also reported as dichotomous variables.

3.2.6 Statistical Analysis

Continuous variables are presented as mean (standard deviation) and categorical variables as proportions for univariate analyses. Bivariate analyses were conducted using t tests, Pearson chi-square tests, Fisher's exact tests, or multiple comparisons with Tukey procedures to examine the relationship between a covariate of interest with ACE inhibitors and/or ARBs, or with intraoperative hypotension (SBP <100mmHg) and its associated treatments and with the outcome of AKI. Logistic regression was performed to assess the crude association between the variables of interest with AKI. Multivariable analyses were conducted between the variables of interest with AKI and adjusted for pre-identified covariates. We selected covariates for adjustment based on clinical knowledge and a literature review. The covariates adjusted for

included age, diabetes, hypertension, pre-existing chronic kidney disease, repair type performed, aneurysm size and SBP < 100mmHg intraoperatively (for the ACE/ARB analysis only). The crude and adjusted associations are estimated with odds ratios and 95% confidence intervals. Two-sided $P<0.05$ was considered statistically significant for all analyses. Analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC, USA).[50] The multivariable models were evaluated for model fit using the Hosmer-Lemeshow goodness-of-fit statistic.[51]

3.2.7 Sensitivity Analysis

To account for multiple centres, we used a mixed effects regression with a random intercept to account for within-centre variability with pre-identified covariates in a multivariable regression model. We compared the regression estimates with the results of those not adjusted for centre.

3.2.8 Subgroup Analyses

1. We examined the effects of ACE inhibitor and/or ARB use within 24 hours of repair and AKI within subgroups of open repair vs. EVAR patients. We used the same methods previously described to determine unadjusted and adjusted odds ratios.

2. We examined the effects of intraoperative hypotension (SBP < 100mmHg) and associated treatments and AKI within subgroups of open repair vs. EVAR patients. We used the same methods previously described to determine unadjusted and adjusted odds ratios.

3. We examined the association between ACE inhibitor and/or ARB use within 24 hours of repair and postoperative AKI within a subgroup of patients who were prescribed

ACE/ARBs preoperatively regardless of whether they were taken or held within 24 hours of repair. We excluded patients who were not prescribed these drugs prior to surgery.

3.2.9 Additional Analyses

We conducted exploratory analyses into potential effect modifiers of any association between AKI and the variables of interest relative to both ACE inhibitors/ARBs and intraoperative hypotension.

1. *Interaction between ACE inhibitors and/or ARBs within 24 hours of repair and preexisting chronic kidney disease (CKD)*

We examined whether the presence of preexisting CKD (defined by a preoperative eGFR <60 mL/min per 1.73m$_2$) modified the effect of ACE inhibitors and/or ARBs prior to AAA repair with respect to the risk of AKI. The *P* value for the interaction was assessed by including the ACE inhibitor and/or ARB variable (yes/no), an indicator variable for CKD (GFR<60 mL/min/1.73m$_2$ vs 60 mL/min/1.73m$_2$) and an interaction variable (CKD x ACE/ARB) as independent variables in a regression model for binary outcome data.

2. *Interaction between SBP < 100mmHg during repair (and associated treatments) and preexisting chronic kidney disease (CKD)*

We examined whether the presence of preexisting CKD (defined by a preoperative eGFR <60 mL/min per 1.73m$_2$) modified the effect of intraoperative hypotension (SBP <100mmHg) and its associated treatments with respect to the risk of AKI. The *P* value for the interaction was assessed by including the SBP <100mmHg variable, an indicator variable for CKD (GFR<60 mL/min/1.73m$_2$ vs 60 mL/min/1.73m$_2$) and an interaction variable (CKD x SBP <100mmHg) as independent variables in a regression model for binary outcome data.

3. *Interaction between SBP < 100mmHg during repair (and associated treatments) and repair type performed (open vs. EVAR)*

We examined whether the repair type performed (open vs. EVAR) modified the effect of SBP < 100mmHg during repair and its associated treatments prior to AAA repair with respect to the risk of AKI. The *P* value for the interaction was assessed by including the SBP < 100mmHg variable, an indicator variable for type of repair (open vs. EVAR) and an interaction variable (repair type x SBP <100mmHg) as independent variables in a logistic regression model.

4. *Mediation Analysis*

We performed a mediation analysis to assess whether having intraoperative SBP less than 100mmHg mediated the effect of ACE inhibitors and/or ARBs within 24 hours of repair on AKI. There is conflicting evidence that suggests intraoperative hypotension is an effect modifier of this association among non-cardiac surgery patients, however, among AAA repair patients intraoperative hypotension was significantly associated with AKI among patients taking ACE inhibitors and/or ARBs.[20–22,52,53] A detailed description of mediation methods are included in Appendix B.

3.3 Results

3.3.1 Descriptive statistics

Table 3-1 shows baseline characteristics of patients undergoing a AAA repair including demographics, comorbidities and laboratory investigations (N=601). The overall sample (N=601) had a mean age of 75.5 years (8.0), ranging from 51 to 95 years and consisted of a higher proportion of males (82.5%) than females (17.5%). The majority of patients underwent

their AAA repair at London Health Sciences Centre (34.4%) and University of Alberta Hospital – Edmonton (29.3%). In terms of comorbidities, most patients had hypertension (76.3%) and many had coronary artery disease (39.0%), were current smokers in the past 30 days (30.8%) or had chronic obstructive pulmonary disease (27.9%) and diabetes mellitus (24.0%). Patients had a mean preoperative serum creatinine of 94.1mol/L (34.2).

Table 3-1 Baseline characteristics of patients undergoing an elective AAA repair.

	Frequency (%)	***Mean (SD)***
Demographics		
Age, years		75.5, (8.0)
Sex, male	496 (82.5%)	
Centre		
London - LHSC	207 (34.4%)	
Edmonton - UAH	176 (29.3%)	
Ottawa - OH	51 (8.5%)	
Hamilton - HHS	51 (8.5%)	
Winnipeg - SBH	34 (5.7%)	
Toronto – SMH	18 (3%)	
Sudbury - HSN	22 (3.7%)	
Toronto – Sunnybrook	16 (2.7%)	
Calgary - PLC	15 (2.5%)	
Montreal - HSC	11 (1.8%)	
Comorbidities		
Congestive heart failure°	27 (4.5%)	
Coronary artery disease	233 (39.0%)	
Chronic obstructive pulmonary disease	165 (27.9%)	
Current smoker (Past 30 days)	185 (30.8%)	
Hypertension	457 (76.3%)	
Diabetes mellitus	144 (24.0%)	
Previous cerebrovascular event	77 (12.9%)	
Pre-existing chronic kidney disease (GFR < 60 mL/min/1.73m2)	191 (31.8%)	
Aneurysm size, mm		58.5, (9.0)
Laboratory Investigations		
Preoperative GFR, mL/min/1.73m2		69.6, (19.6)
Preoperative serum creatinine, mol/L		94.1, (34.2)

N=601

°1 patient missing congestive heart failure information, 3 patients missing coronary artery disease information, 10 patients missing chronic obstructive pulmonary disease information, 1 patient missing current smoker information, 2 patients missing hypertension information, 4 patients missing previous cerebrovascular event information.

SD, standard deviation, LHSC, London health sciences centre, OH, Ottawa hospital, SMH, St. Michael's hospital, HSN, health sciences north, UAH, university of Alberta, PLC, Peter Lougheed centre, SBH, St. Boniface hospital, HHS, Hamilton health sciences, HSC, health sciences centre, GFR, glomerular filtration rate.

Table 3-2 presents operative details of patients undergoing an AAA repair including characteristics specific to open and endovascular repair. The type of repair performed was fairly evenly split with 46.9% of patients undergoing an open repair and 53.1% of patients undergoing an endovascular repair. Of the open repair group most patients had their clamp in the infrarenal position (75.8%) and an overall mean of 55 minutes (28.1). Of the endovascular repair group fluoroscopy was used among 96.5% of patients with an overall mean duration of 12.7 minutes (21.8).

Table 3-2 Operative details of patients undergoing an AAA repair

	Frequency (%)	***Mean (SD)***
Type of repair performed		
Open	282 (46.9%)	
Endovascular	319 (53.1%)	
Blood transfusion, units		1.5, (3.2)
IV contrast	315 (52.7%)	
Renal revascularization	50 (9.2%)	
Lower limb revascularization	63 (11.7%)	
Mannitol	34 (5.7%)	
Furosemide	9 (1.5%)	
Open Repair Only (N=282)		
Clamp position*		
Above and Below	21 (7.6%)	
Infrarenal	210 (75.8%)	
Suprarenal	46 (16.6%)	
Cross clamp duration, minutes		55, (28.1)
Cell saver blood, mL		640.6, (595.7)
Endovascular Repair Only (N=319)		
Fluoroscopy used	302 (96.5%)	
Fluoroscopy time, minutes		12.7, (21.8)

N=601

3 patients missing IV contrast information , 58 patients missing renal revascularization information, 62 patients missing lower limb revascularization information, 3 patients missing mannitol information, 8 patients missing furosemide information, *5 patients missing clamp position, 6 patients missing fluoroscopy information.
SD, standard deviation, IV, intravenous.

Clinical outcomes of all 601 patients are described in Table 3-3. AKI developed postoperatively in 13.1% of all patients by 7 days postoperatively. There were 4 competing events of death in the overall sample. Patients who developed postoperative AKI were classified according to 3 stages with most falling in Class 1, at 74.8% of those who developed AKI. A total of 79 patients were diagnosed with AKI in the first 7 days postoperatively and were classified according to the "KDIGO – kidney disease improving global outcomes" criteria.[5] Dialysis was a rare outcome with 6 patients requiring this intervention (1.0%) and of the overall sample 14 died (2.3%), 9 of which died within 30 days of surgery (1.5%). The mean hospital stay was 5.8 days (5.4).

Table 3-3 Clinical outcomes of patients who underwent an AAA repair

	Frequency (%)	**Mean (SD)**
Acute kidney injury (KDIGO)		
Total	79 (13.1%)	
Stage 1	59 (9.8%)	
Stage 2	11 (1.8%)	
Stage 3	9 (1.5%)	
Dialysis	6 (1.0%)	
Death	14 (2.3%)	
30 days after surgery*	9 (1.5%)	
Other Complications		
Myocardial infarction	19 (3.2%)	
Sepsis/Infection	6 (1.0%)	
Pneumonia	7 (1.2%)	
Major bleed	15 (2.5%)	
Peptic ulcer	3 (0.5%)	
Non-fatal cardiac arrest	5 (0.8%)	
Stroke	2 (0.3%)	
Deep vein thrombus	1 (0.2%)	
Pulmonary embolus	4 (0.7%)	
Congestive heart failure	7 (1.2%)	
Lower limb amputation	1 (0.2%)	
Ischemic bowel	4 (0.7%)	
Hospital stay, days		5.8, (5.4)

N=601

*5 patients missing "death 30 days after surgery" information.

SD, standard deviation, KDIGO, kidney disease improving global outcomes.

Characteristics of patients with (N=79) and without postoperative AKI (N=522) are described in Appendix C. Patients without AKI were significantly older than patients with AKI. Patients without AKI were significantly more likely to be male than patients with AKI. Patients with AKI were significantly more likely to have preoperative hypertension than patients without AKI . Patients with AKI were significantly more likely to have an open repair, rather than an endovascular repair. Patients with AKI were significantly more likely to have pre-existing CKD than patients without AKI. Patients who developed postoperative complications were significantly more likely to have also developed postoperative AKI. Patients who developed postoperative AKI had significantly higher mortality than those who didn't develop AKI.

3.3.2 ACE inhibitors and/or ARBs

The data set used to analyze ACE inhibitors and/or ARBs with postoperative AKI are comprised of a sample of 599 patients. The demographics, comorbidities, laboratory measurements, operative details and outcomes are summarized in Table 3-4. Patients who took ACE inhibitors and/or ARBs in the 24 hours prior to repair were significantly more likely to also have preoperative diabetes mellitus compared with patients who did not take ACE inhibitors and/or ARBs in the 24 hours prior to repair. Patients with preoperative hypertension were significantly more likely to receive ACE inhibitors and/or ARBs in the 24 hours prior to repair compared with those who did not receive them. Patients with preoperative congestive heart failure were also significantly more likely to take ACE inhibitors and/or ARBs in the 24 hours prior to repair compared to those that did not. Patients who took ACE inhibitors and/or ARBs in the 24 hours prior to AAA repair were not significantly more at risk for AKI however they had significantly higher mortality.

Table 3-4. Baseline Demographics of patients taking ACE inhibitors and/or ARBs or not taking ACE inhibitors and/or ARBs in the 24 hours prior to AAA repair

	ACE/ARB (yes) N=172	ACE/ARB (no) N=427	*P* Value
Demographics			
Age (years) mean, SD	75.9, 7.5	75.4, 8.1	0.51
Sex, male No. (%)	147 (85.5%)	347 (81.3%)	0.22
Comorbidities			
DM No. (%)	56 (32.6%)	86 (20.1%)	0.001
HTN No. (%)	165 (95.9%)	292 (68.4%)	<0.0001
CHF° No. (%)	15 (8.8%)	12 (2.8%)	<0.01
CAD No. (%)	76 (44.7%)	156 (36.6%)	0.07
COPD No. (%)	44 (26.0%)	120 (28.6%)	0.54
Previous CVE No. (%)	29 (17.1%)	48 (11.3%)	0.06
Current Smoker (Past 30 days) No. (%)	49 (28.5%)	136 (31.9%)	0.41
Pre-existing chronic kidney disease (GFR < 60 mL/min/1.73m2)	60 (34.9%)	131 (30.7%)	0.32
SCr (μmol/L) mean, SD	96.0, 32.3	93.4, 35.1	0.41
eGFR categories (mL/min/1.73m2) No. (%)	0.553		
<30	4 (2.3%)	15 (3.5%)	
30 to 45	18 (10.5%)	39 (9.2%)	
46 to 60	38 (22.1%)	77 (18.0%)	
>60	112 (65.1%)	296 (69.3%)	
Operative Details			
Type of repair No. (%)			
Open	74 (43.0%)	207 (48.5%)	0.23
EVAR	98 (57.0%)	220 (51.5%)	
Aneurysm size (mm) mean, SD	56.5, 14.1	58, 10.4	0.24
Outcomes			
AKI – Total	28 (16.3%)	51 (11.9%)	0.16
Stage 1	21 (12.2%)	38 (8.9%)	
Stage 2	2 (1.2%)	9 (2.1%)	0.15
Stage 3	5 (2.9%)	4 (0.9%)	
Complications** No. (%)	17 (9.9%)	37 (8.7%)	0.64
Death*** No. (%)	6 (3.5%)	3 (0.7%)	0.02

°1 patient missing CHF information, 3 patients missing CAD information, 10 patients missing COPD information, 4 patients missing previous CVE information, 1 patient missing current smoker information, 5 patients missing death information. , **Complications include new acute dialysis, myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft, sepsis, pneumonia, non-fatal cardiac arrest, stroke, deep vein thrombosis,

pulmonary embolism, lower limb amputation, ischemic bowel, congestive heart failure, death within 30 days of surgery), *** death within 30 days of surgery.
ACE, angiotensin-converting enzyme inhibitor, ARB, angiotensin II receptor blocker, AAA, abdominal aortic aneurysm repair, SD, standard deviation, No. number, DM, diabetes mellitus, HTN, hypertension, CHF, congestive heart failure, CAD, coronary artery disease, COPD, chronic obstructive pulmonary disease, CVE, cerebrovascular event, SCr, serum creatinine, GFR, glomerular filtration rate, AKI, acute kidney injury.

3.3.3 Intraoperative hypotension: SBP <100mmHg

The data set used to analyze SBP < 100mmHg and its associated treatments with postoperative AKI were comprised of a sample of 593 patients. The demographics, comorbidities, laboratory measurements and operative details are summarized in Table 3-5. Patients who had an intraoperative SBP < 100mmHg and were treated with fluids were significantly more likely to be older compared with patients who did not have an intraoperative SBP < 100mmHg. Repair type performed and intraoperative SBP < 100mmHg treatment were significantly related. Of the 157 patients that did not have an intraoperative SBP < 100mmHg, 77.7% of them had an EVAR. Aneurysm size (mm) and SBP < 100mmHg with associated treatments were significantly related. Patients who had intraoperative SBP < 100mmHg were significantly more at risk for AKI compared with patients who had SBP > 100mmHg. Patients treated with vasopressors comprised 50% of the 79 patients with AKI.

Table 3-5. Baseline demographics of patients with intraoperative hypotension (SBP <100mmHg) during AAA repair

	SBP > 100mmHg	SBP < 100mmHg			
	N=157	**No Treatment N=85**	**Fluids N=108**	**Inotropes/ Vasopressors N=243**	***P* Value**
Demographics					
Age mean, SD	77.2, 7.7	74.5, 7.9	74.5, 7.8	75.3, 8.1	0.02 (2 vs 0)
Sex male No. (%)	132 (84.1%)	70 (82.4%)	87 (80.6%)	201 (82.7%)	0.91
Comorbidities					
DM No. (%)	39 (24.8%)	22 (25.9%)	24 (22.2%)	55 (22.6%)	0.89
HTN No. (%)	123 (78.3%)	70 (82.4%)	84 (77.8%)	175 (72.0%)	0.20
CHF° No. (%)	11 (7.1%)	3 (3.5%)	2 (1.9%)	11 (4.5%)	0.26
CAD No. (%)	61 (39.4%)	34 (40.5%)	36 (33.3%)	101 (41.6%)	0.54
COPD No. (%)	53 (34.2%)	24 (29.3%)	31 (29.3%)	55 (22.8%)	0.10
Previous CVE No. (%)	27 (17.2%)	11 (13.3%)	8 (7.5%)	31 (12.8%)	0.15
Current smoker (Past 30 days) No. (%)	39 (24.8%)	28 (33.3%)	37 (34.3%)	79 (32.5%)	0.28
Pre-existing chronic kidney disease	58 (36.9%)	22 (25.9%)	29 (26.9%)	79 (32.5%)	0.21
Laboratory Measurements					
SCr (μmol/L) mean, SD	96.7, 37.2	90.9, 27.8	88.2, 27.2	95.7, 34.9	0.13
eGFR categories (mL/min/1.73m2) No. (%)					
<30	5 (3.2%)	1 (1.2%)	1 (0.9%)	11 (4.5%)	0.38
30 to 45	16 (10.2%)	10 (11.8%)	9 (8.3%)	21 (8.6%)	
46 to 60	37 (23.6%)	11 (12.9%)	19 (17.6%)	47 (19.3%)	
>60	99 (63.1%)	63 (74.1%)	79 (73.2%)	164 (67.5%)	
Operative Details					
Type of repair No. (%)					
Open	35 (22.3%)	45 (52.9%)	64 (59.3%)	131 (53.9%)	<0.0001
EVAR	122 (77.7%)	40 (47.1%)	44 (40.7%)	112 (46.1%)	
Aneurysm size (mm) mean, SD	55.5, 11.6	56.8, 14.1	57.7, 12.5	59.2, 9.1	0.02 (3 vs 0)

Outcomes					
AKI – Total	11 (7.0%)	15 (17.7%)	12 (11.1%)	38 (15.6%)	0.04
Stage 1	9 (5.7%)	10 (11.8%)	8 (7.4%)	31 (12.8%)	
Stage 2	0 (0%)	4 (4.7%)	3 (2.8%)	3 (1.2%)	0.07
Stage 3	2 (1.3%)	1 (1.2%)	1 (0.9%)	4 (1.7%)	
Complications** No. (%)	10 (6.4%)	11 (12.9%)	6 (5.6%)	24 (9.9%)	0.19
Death*** No. (%)	2 (1.3%)	3 (3.5%)	0 (0%)	2 (0.8%)	0.13

°1 patient missing CHF information, 3 patients missing CAD information, 9 patients missing COPD information, 4 patients missing previous CVE information, 5 patients missing death information. , **Complications include new acute dialysis, myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft, sepsis, pneumonia, non-fatal cardiac arrest, stroke, deep vein thrombosis, pulmonary embolism, lower limb amputation, ischemic bowel, congestive heart failure, death within 30 days of surgery), *** death within 30 days of surgery. SBP, systolic blood pressure, AAA, abdominal aortic aneurysm repair, SD, standard deviation, No. number, DM, diabetes mellitus, HTN, hypertension, CHF, congestive heart failure, CAD, coronary artery disease, COPD, chronic obstructive pulmonary disease, CVE, cerebrovascular event, SCr, serum creatinine, eGFR, estimated glomerular filtration rate, EVAR, endovascular, AKI, acute kidney injury.

3.3.4 Bivariate and Multivariable Logistic Regression Models

Table 3-6 presents the results of the multivariable models for ACE inhibitors and/or ARBs and for intraoperative SBP < 100mmHg. The ACE inhibitors and/or ARBs model was adjusted for age, pre-existing CKD, repair type performed (open vs. EVAR), diabetes, hypertension, intraoperative SBP < 100mmHg and aneurysm diameter. These variables were chosen as they are based on substantive theory from clinical knowledge and literature review. Diabetes and hypertension were significantly associated with ACE inhibitors and/or ARBs. ACE inhibitors and/or ARBs were not significantly independently associated with AKI. The 95% CI of 0.8 to 2.2 spans 1.0, therefore the increased odds (OR 1.3) of AKI among patients who took ACE inhibitors and/or ARBs within 24 hours of repair compared with patients who did not was not statistically significant. Neither the crude nor adjusted odds ratio were statistically significant. The ACE inhibitor and/or ARB model fit the data satisfactorily with a nonsignificant Hosmer-Lemeshow goodness-of-fit test (P=0.54). Bivariate analyses determined statistically significant associations between select treatments for intraoperative hypotension and AKI postoperatively. Patients who did not receive treatment for SBP <100mmHg during repair had 2.8 (95% CI 1.2-

6.5) greater odds of postoperative AKI compared with those who maintained SBP > 100mmHg in the bivariate logistic regression. Patients who received inotropes or vasopressors for SBP <100mmHg during repair had 2.5 (95% CI 1.2-5.0) greater odds of postoperative AKI compared with those who maintained SBP > 100mmHg in the bivariate logistic regression. The bivariate analyses did not detect a significant association between fluid treatment of intraoperative hypotension and postoperative AKI. The intraoperative SBP <100mmHg and associated treatments model was adjusted for age, pre-existing CKD, repair type performed (open vs. EVAR), diabetes, hypertension and aneurysm diameter. These variables were also chosen based on substantive theory from clinical knowledge and literature review. Age, type of repair and aneurysm size (mm) were significantly associated with type of treatment for intraoperative hypotension. None of the levels of the SBP <100mmHg exposure variable was significantly independently associated with AKI in the multivariable analyses. The 95% CI for all 3 levels of odds ratios include 1.0, therefore the increased odds of AKI among patients who received fluids, inotropes/vasopressors or no treatment for an intraoperative SBP < 100mmHg compared with patients with intraoperative SBP >100mmHg was not statistically significant. The SBP model fit the data satisfactorily with a nonsignificant Hosmer-Lemeshow goodness-of-fit test (P=0.43). The assessment of multicollinearity for each model produced variance inflation factors all lower than two indicating no concern regarding this assumption for multivariable logistic regression.

Table 3-6 Bivariate and Multivariable Logistic Regression of ACE inhibitors and/or ARBs and SBP < 100mmHg and AKI

Exposure		Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
ACE/ARB*		1.4 (0.9 – 2.4)	1.3 (0.8 – 2.2)
SBP < 100mmHg**			
	No treatment	2.8 (1.2-6.5)	2.0 (0.8 – 4.8)
	Fluids	1.7 (0.7-3.9)	1.0 (0.4 – 2.6)
	Inotropes/Vasopressors	2.5 (1.2-5.0)	1.7 (0.8 – 3.7)

* Adjusting for Age, Pre-existing CKD, Repair Type Performed (Open vs. EVAR), DM, HTN, intraoperative SBP < 100 mmHg, and Aneurysm Diameter
** Adjusting for Age, Pre-existing CKD, Repair Type Performed (Open vs. EVAR), DM, HTN, and Aneurysm Diameter
ACE, angiotensin-converting enzyme inhibitor, ARB, angiotensin II receptor blocker, SBP, systolic blood pressure, AKI, acute kidney injury, CI, confidence interval, CKD, chronic kidney disease, EVAR, endovascular abdominal aortic aneurysm repair, DM, diabetes mellitus, HTN, hypertension.

3.3.5 Sensitivity Analysis

The adjusted odds ratios further adjusted to account for centre are summarized in Appendix D contrasted with the adjusted odds ratio without accounting for centre. The odds ratios and 95% CI remain relatively similar indicating that centre did not significantly affect the results of the multivariable analyses.

3.3.6 Subgroup Analysis

Among 275 open repair patients, 58 patients developed postoperative AKI. Among 318 EVAR patients, 18 developed postoperative AKI. Therefore, the multivariable results should be interpreted with extreme caution as there were too few events per variable. Table 3-7 and 3-8 presents that none of the point estimates, neither crude nor adjusted, was statistically significant as they were underpowered to detect a difference. However, the point estimates for no treatment and inotropes/vasopressors was higher in open repair patients compared with EVAR patients. Among EVAR patients, the odds ratio for inotropes/vasopressors suggests a potentially

protective effect against AKI (OR 0.8 95% CI 0.3 – 2.5) compared with patients who did not have intraoperative hypotension (SBP < 100mmHg) as shown in Table 3-8.

Table 3-7. Crude and Adjusted Odds Ratios of ACE inhibitors and/or ARBs and Intraoperative Hypotension (SBP < 100mmHg) and AKI among Open Repair Patients

Exposure		Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
ACE/ARB*		1.4 (0.8 – 2.7)	1.5 (0.5 – 4.1)
SBP < 100mmHg**			
	No treatment	2.8 (0.8 – 9.7)	3.4 (0.8 – 4.8)
	Fluids	1.4 (0.4 – 5.0)	1.7 (0.5 – 5.9)
	Inotropes/Vasopressors	2.5 (0.8 – 7.6)	2.8 (0.9 – 9.0)

* Adjusting for Age, Pre-existing CKD, DM, HTN, intraoperative SBP < 100 mmHg, and Aneurysm Diameter
** Adjusting for Age, Pre-existing CKD, DM, HTN, and Aneurysm Diameter
ACE, angiotensin-converting enzyme inhibitor, ARB, angiotensin II receptor blocker, SBP, systolic blood pressure, AKI, acute kidney injury, CI, confidence interval, CKD, chronic kidney disease, EVAR, endovascular abdominal aortic aneurysm repair, DM, diabetes mellitus, HTN, hypertension.

Table 3-8. Crude and Adjusted Odds Ratios of ACE inhibitors and/or ARBs and Intraoperative Hypotension (SBP < 100mmHg) and AKI among EVAR Patients

Exposure		Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
ACE/ARB*		1.9 (0.7 – 4.9)	1.2 (0.6 – 2.4)
SBP < 100mmHg**			
	No treatment	1.3 (0.3 – 5.4)	1.3 (0.3 – 5.5)
	Fluids	0.8 (0.2 – 3.9)	0.6 (0.1 – 3.3)
	Inotropes/Vasopressors	0.9 (0.3 – 2.9)	0.8 (0.3 – 2.5)

* Adjusting for Age, Pre-existing CKD, DM, HTN, intraoperative SBP < 100 mmHg, and Aneurysm Diameter
** Adjusting for Age, Pre-existing CKD, DM, HTN, and Aneurysm Diameter
ACE, angiotensin-converting enzyme inhibitor, ARB, angiotensin II receptor blocker, SBP, systolic blood pressure, AKI, acute kidney injury, CI, confidence interval, CKD, chronic kidney disease, EVAR, endovascular abdominal aortic aneurysm repair, DM, diabetes mellitus, HTN, hypertension.

Of the 599 patients included in the overall patient sample, 358 patients were prescribed ACE inhibitors or ARBs prior to surgery. Among those 358 patients prescribed ACE inhibitors or ARBs prior to surgery, 172 patients received ACE/ARBs within 24 hours prior to repair and 186 patients did not receive ACE/ARBs within 24 hours prior to repair (i.e. they were held). In a subgroup analysis of the 358 patients prescribed ACE/ARBs preoperatively, 51 patients

developed postoperative AKI. Therefore, the multivariable results should be interpreted with extreme caution as there were too few events per variable. Table 3-9 presents that none of the point estimates, neither crude nor adjusted, was statistically significant as they were underpowered to detect a difference.

Table 3-9. Crude and Adjusted Odds Ratios of ACE inhibitors and/or ARBs and AKI among patients prescribed ACE inhibitors and/or ARBs prior to surgery

Exposure	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
ACE/ARB*	1.4 (0.8 – 2.5)	1.6 (0.8 – 2.9)

* Adjusting for Age, Pre-existing CKD, DM, HTN, intraoperative SBP < 100 mmHg, and Aneurysm Diameter

3.3.7 Additional Analyses

The possible interaction between intraoperative hypotension treatments and type of repair performed was not statistically significant (*P*=0.4, *P*=0.5, *P*=0.2). The possible interaction between ACE inhibitor and/or ARB use within 24 hours of repair and pre-existing chronic kidney disease was not statistically significant (*P*=0.98). The possible interaction between intraoperative hypotension treatments and pre-existing chronic kidney disease was not statistically significant (*P*=0.5, *P*=0.9, *P*=0.6).

The results of the mediation analysis of ACE inhibitors and/or ARBs effect on AKI mediated by SBP <100mmHg during repair are presented in Table 3-10. The estimated direct effect odds ratio of ACE inhibitor and/or ARB use was 1.3 and the indirect effect mediated by SBP <100mmHg during repair was 1.0. Large sample (Wald) and bootstrap (1000) confidence intervals are provided. None of the effects was statistically significant. 3.7% of the total effect of treatment was mediated by SBP <100mmHg during repair, however again these results were not statistically significant and cannot be interpreted.

Table 3-10. Mediation analysis of ACE inhibitors and/or ARBs effect on AKI mediated by SBP <100mmHg during repair

	Estimate	Wald 95% Confidence Interval	Bootstrap 95% Confidence Interval	*P* value
Odds ratio total effect (TE)	1.3	0.6-2.0	0.7-2.3	0.41
Odds ratio natural direct effect (NDE)	1.3	0.6-2.0	0.7-2.3	0.42
Odds ratio natural indirect effect (NIE)	1.0	0.97-1.04	0.98-1.07	0.62
Percentage mediated (%)	3.7	-11.9-19.4	-7.8-510.7	0.64

ACE, angiotensin-converting enzyme inhibitor, ARB, angiotensin II receptor blocker, SBP, systolic blood pressure, AKI, acute kidney injury,

3.4 Discussion

Among patients undergoing AAA repair taking an ACE inhibitor and/or ARB within 24 hours prior to repair, we observed no significant association in the odds of postoperative AKI in users compared to non-users. Among patients undergoing AAA repair who had intraoperative hypotension (SBP < 100mmHg) and received either fluids, inotropes/vasopressors or no treatment, we observed that patients who were treated with inotropes/vasopressors had higher odds of AKI when compared to those without hypotension. Patients who received no treatment also had higher odds of AKI compared with patients who did not experience intraoperative hypotension. Among patients who were treated with fluids, we observed no statistically significant association in the odds of postoperative AKI compared with patients who did not experience hypotension. After adjustment for pre-identified covariates none of the odds ratios was statistically significant, however the direction of effect remained the same suggesting a

possible trend of an association between patients who received inotropes/vasopressors or no treatment for intraoperative hypotension with AKI compared with patients who did not experience intraoperative hypotension. These results were not statistically significant and were underpowered to detect a difference. Patients who have prolonged hypotension are conceivably at increased risk for AKI through the development of acute tubular necrosis due to hypoperfusion.[40] The addition of inotropes and vasopressors may further exacerbate this through vasoconstriction of the arterioles at the nephron level.[40] It is conceivable that the association we observed in the un-adjusted analysis has a biologic rationale and may require further work with a larger dataset to substantiate the claim. Our data suggests the possibility that intraoperative hypotension may be treated with fluids preferentially over inotropes/vasopressors to prevent AKI, but this needs to be further evaluated in a dedicated, well powered RCT.

This study performed a secondary data analysis of an RCT of patients who underwent an AAA repair. The frequency of AKI among the 601 patients included was 13.1%, which falls within the range of incidences reported in most studies.[1–6,8,10] In our analysis we found age, sex, hypertension, pre-existing chronic kidney disease, and open repair type to be significantly associated with AKI. Patients with AKI were also more likely to have other postoperative complications and had higher mortality. Our bivariate and multivariable logistic regression of ACE inhibitor and/or ARB use did not demonstrate a statistically significant association with AKI in either analysis (OR_{crude}=1.4 95% CI 0.9-2.4, $OR_{adjusted}$=1.3 95% CI 0.8-2.2). There is conflicting evidence as to whether these drugs increase or decrease the risk of AKI among AAA repair patients and there is no clear consensus on whether to hold or give the drugs in the preoperative period.[5,11,28,29,49] Among vascular surgery patients, holding ACE/ARB preoperatively has been suggested amongst a few cohort studies.[29,49] Zabrocki et al. determined a

nonsignificant association between use of ACE/ARBs in the preoperative setting and open vs EVAR in a retrospective cohort study of 268 AAA repair patients.[6] Pisimisis et al found a trend towards an association between ACE inhibitors and AKI among 208 EVAR patients in a retrospective cohort study.[29] Bertrand et al performed a RCT of 37 vascular surgery patients randomized to discontinued ACE/ARBs on the day before surgery vs ACE/ARBs given 1 hour before surgery and they recommend discontinuing the drugs on the day before surgery.[21] Statius van eps et al determined a significant association between ACE/ARB use and postoperative AKI (OR 4.1 95% CI 1.4 – 12.1) among a retrospective cohort 212 EVAR patients.[11] Interaction between ACE inhibitors and/or ARBs and pre-existing CKD on AKI was not statistically significant. Intraoperative hypotension did not demonstrate a statistically significant result as a mediator between ACE inhibitors and/or ARBs within 24 hours of repair and postoperative AKI. This is in contrast to prior literature that showed a significant association, however, a systematic review of noncardiac surgery patients failed to come to a conclusion as to whether or not to hold ACE inhibitors and/or ARBs prior to surgery to prevent AKI and other major complications.[20–22,52,53] Our data would suggest that holding ACE inhibitors/ARBs is not necessary, however, we acknowledge the limitations of our analysis such that although we could separate those patients who were not on the drugs prior to surgery from those that simply held the drug the day before surgery, our analysis was underpowered to detect a difference.

Our multivariable logistic regression analyses of intraoperative hypotension (SBP <100mmHg) treatments and AKI were not statistically significant. However, the crude odds ratios from the bivariate analyses for inotrope/vasopressors (OR_{crude}=2.5 95% CI 1.2-5.0, $OR_{adjusted}$=1.7 95% CI 0.8-3.7) or no treatment (OR_{crude}=2.8 95% CI 1.2-6.5, $OR_{adjusted}$=2.0 95% CI 0.8-4.8) were statistically significant and although the adjusted odds ratio were not, the direction of effect

remained unchanged. The confidence intervals for these two adjusted point estimates are wide indicating that further studies of these effects could be done with larger sample sizes to determine a precise estimate. Interaction between intraoperative hypotension and pre-existing CKD on AKI was not statistically significant. Interaction between intraoperative hypotension and repair type performed on postoperative AKI was not statistically significant. This is in contrast to relevant studies that demonstrated a statistically significant association between intraoperative hypotension and AKI among AAA repair patients.[2,33,34] Among open repair patients, Tallgren et al. (N=69), Davidovic et al. (N=450), and Brinkman et al.(N=40) all determined a significant association between intraoperative hypotension and AKI in prospective and retrospective cohort studies.[2,34,35] Brinkman et al. found a significant association between duration and severity of intraoperative hypotension and postoperative AKI in a pilot prospective observational trial of 40 patients undergoing open AAA repair (P=0.04, P=0.01).[34] Yue et al. found intraoperative hypotension to be a significant predictor of AKI in a retrospective cohort of 71 critically ill open and EVAR AAA repair patients (OR 6.0 95% CI 1.2 – 30.7).[33] However, Macedo et al found no significant differences in rates of hypotension and AKI during open repair of thoracoabdominal and AAA repair in a cohort of 77 patients.[45] To our knowledge, our study is the first analysis of intraoperative hypotension's associated treatments and postoperative AKI among AAA repair patients.

Efforts to reduce postoperative AKI would be beneficial in this patient setting to minimize risk of further morbidities and mortality. The target areas of this analysis were use of ACE inhibitors and/or ARBs within 24 hours prior to repair and intraoperative hypotension (SBP <100mmHg) and associated treatments. The results of this analysis add to the existing research available to provide further guidance on best practice among AAA repair patients. Unfortunately, no solid

significant associations were identified, and further research is required to inform evidence-based decision making.

Our study has many strengths. The data used for this analysis were prospectively collected in the largest randomized controlled trial among AAA repair studies. The RCT minimized outcome misclassification using adjudicated outcomes. The results are generalizable across Canada as the RCT was conducted in multiple centres. This was one of the first studies to look at treatments for intraoperative hypotension which is a proposed area of future interest amongst prior research. Our results were limited by a lack of power for the analyses. The definition of intraoperative hypotension could have been further limited to more severe measures of SBP; however, we were limited by the available data in the RCT. We also looked at intraoperative hypotension as a sole measure rather than trends during the repair to consider duration and further granularity of this metric may have provided us with more insight into its potential relationship with AKI. The dose of ACE inhibitors or ARBs was also not taken into consideration and this may have further modified their effect.

3.5 Conclusion

We found no evidence to suggest that there is a statistically significant association between patients who received an ACE inhibitor and/or ARB within 24 hours of repair and postoperative AKI compared with patients who did not. Our results suggest there may be an association between intraoperative hypotension, its method of treatment and AKI however this is not conclusive and worthy of further study in a RCT.

3.6 References

1. Dubois L, Durant C, Harrington DM, Forbes TL, Derose G, Harris JR. Technical factors are strongest predictors of postoperative renal dysfunction after open transperitoneal juxtarenal abdominal aortic aneurysm repair. J Vasc Surg. 2013;57(3):648–54.

2. Tallgren M, Niemi T, Poyhia R, Raininko E, Railo M, Salmenpera M, et al. Acute renal injury and dysfunction following elective abdominal aortic surgery. Eur J Vasc Endovasc Surg. 2007;33(5):550–5.

3. Saratzis AN, Goodyear S, Sur H, Saedon M, Imray C, Mahmood A. Acute kidney injury after endovascular repair of abdominal aortic aneurysm. J Endovasc Ther. 2013;20(3):315–30.

4. Tang Y, Chen J, Huang K, Luo D, Liang P, Feng M, et al. The incidence, risk factors and in-hospital mortality of acute kidney injury in patients after abdominal aortic aneurysm repair surgery. BMC Nephrol. 2017;18(1):184.

5. KDIGO. Clinical practice guideline for acute kidney injury (AKI). Kidney Int Suppl. 2012;2(1):4.

6. Zabrocki L, Marquardt F, Albrecht K, Herget-Rosenthal S. Acute kidney injury after abdominal aortic aneurysm repair: current epidemiology and potential prevention. Int Urol Nephrol. 2018;50(2):331–7.

7. Wald R, Waikar SS, Liangos O, Pereira BJG, Chertow GM, Jaber BL. Acute renal failure after endovascular vs open repair of abdominal aortic aneurysm. J Vasc Surg. 2006;43(3):466.

8. Dariane C, Coscas RR, Boulitrop C, Javerliat I, Vilaine E, Goeau-Brissonniere O, et al. Acute kidney injury after open repair of intact abdominal aortic aneurysms. Ann Vasc Surg. 2017;39(November 2016):294–300.

9. Minami K, Sugiyama Y, Iida H. A retrospective observational cohort study investigating

the association between acute kidney injury and all-cause mortality among patients undergoing endovascular repair of abdominal aortic aneurysms. J Anesth. 2017;31(5):686–91.

10. Saratzis A, Melas N, Mahmood A, Sarafidis P. Incidence of acute kidney injury (AKI) after endovascular abdominal aortic aneurysm repair (EVAR) and impact on outcome. Eur J Vasc Endovasc Surg. 2015;49(5):534–40.

11. Statius van Eps RG, Nemeth B, Mairuhu RTA, Wever JJ, Veger HTC, van Overhagen H, et al. Determinants of acute kidney injury and renal function decline after endovascular abdominal aortic aneurysm repair. Eur J Vasc Endovasc Surg. 2017;54(6):712–20.

12. Bang J-YY, Lee JB, Yoon Y, Seo H-SS, Song JG-G, Hwang GS. Acute kidney injury after infrarenal abdominal aortic aneurysm surgery: a comparison of AKIN and RIFLE criteria for risk prediction. Br J Anaesth. 2014;113(6):993–1000.

13. Shah M, Jain AK, Brunelli SM, Coca SG, Devereaux PJ, James MT, et al. Association between angiotensin converting enzyme inhibitor or angiotensin receptor blocker use prior to major elective surgery and the risk of acute dialysis. BMC Nephrol. 2014;15(1):1–9.

14. Cheungpasitporn W, Thongprayoon C, Srivali N, O'Corragain OA, Edmonds PJ, Ungprasert P, et al. Preoperative renin-angiotensin system inhibitors use linked to reduced acute kidney injury: a systematic review and meta-analysis. Nephrol Dial Transplant. 2015;30(6):978–88.

15. Yacoub R, Patel N, Lohr JW, Rajagopalan S, Nader N, Arora P. Acute kidney injury and death associated with renin angiotensin system blockade in cardiothoracic surgery: A meta-analysis of observational studies. Am J Kidney Dis. 2013;62(6):1077–86.

16. Spatz C, Saadulla L, Lapsiwala A, Parhizgar A, Ghahramani N. Effect of renin-angiotensin-aldosterone system blockade therapy on incidence of contrast-induced nephropathy in patients with chronic kidney disease. Iran J Kidney Dis. 2012;6(6):432–6.

17. Drake TM, Cheung LK, Gaba F, Glasbey J, Griffiths N, Helliwell RJ, et al. Association between peri-operative angiotensin-converting enzyme inhibitors and angiotensin-2

receptor blockers and acute kidney injury in major elective non-cardiac surgery: a multicentre, prospective cohort study. Anaesthesia. 2018;73(10):1214–22.

18. Nadim MK, Forni LG, Bihorac A, Hobson C, Koyner JL, Shaw A, et al. Cardiac and vascular surgery-associated acute kidney injury: The 20th international consensus conference of the ADQI (acute disease quality initiative) group. J Am Heart Assoc. 2018;7(11).

19. Barodka V, Silvestry S, Zhao N, Jiao X, Whellan DJ, Diehl J, et al. Preoperative renin-angiotensin system inhibitors protect renal function in aging patients undergoing cardiac surgery. J Surg Res. 2011;167(2):e63–9.

20. Alabdan N, Gosmanova EO, Tran NQT, Oliphant CS, Pan H, Broyles JE, et al. Acute kidney injury in patients continued on renin-angiotensin system blockers during hospitalization. Am J Med Sci. 2017;353(2):172–7.

21. Bertrand M, Godet G, Meersschaert K, Salcedo E, Coriat P. Should the angiotensin II antagonists be discontinued. Anesth Analg. 2001;92:26–30.

22. Ling Q, Gu Y, Chen J, Chen Y, Shi Y, Zhao G, et al. Consequences of continuing renin angiotensin aldosterone system antagonists in the preoperative period: a systematic review and meta-analysis. BMC Anesthesiol. 2018;18(1):26.

23. Coca SG, Garg AX, Swaminathan M, Garwood S, Hong K, Thiessen-Philbrook H, et al. Preoperative angiotensin-converting enzyme inhibitors and angiotensin receptor blocker use and acute kidney injury in patients undergoing cardiac surgery. Nephrol Dial Transplant. 2013;28(11):2787–99.

24. Peng F, Su J, Lin J, Niu W. Impact of renin-angiotensin-aldosterone system-blocking agents on the risk of contrast-induced acute kidney injury: a prospective study and meta-analysis. J Cardiovasc Pharmacol. 2015;65(3):262–8.

25. Goo J-J, Kim J-J, Kang J-H, Kim K-N, Byun K-S, Kim M, et al. Effect of renin-angiotensin-system blockers on contrast-medium-induced acute kidney injury after coronary angiography. Korean J Intern Med. 2014;29(2):203–9.

26. Mansfield KE, Nitsch D, Smeeth L, Bhaskaran K, Tomlinson LA. Prescription of renin-angiotensin system blockers and risk of acute kidney injury: a population-based cohort study. BMJ Open. 2016;6(12):e012690.

27. Lim HJ, Lee HH, Kim AJ, Ro H, Kim HS, Chang JH, et al. Renin-angiotensin-aldosterone system blockade in critically ill patients is associated with increased risk for acute kidney injury. Tohoku J Exp Med. 2016;238(1):17–23.

28. Tagawa M, Ogata A, Hamano T. Pre- and/or intra-operative prescription of diuretics, but not renin-angiotensin-system inhibitors, is significantly associated with acute kidney injury after non-cardiac surgery: A retrospective cohort study. PLoS One. 2015;10(7):e0132507.

29. Pisimisis GT, Bechara CF, Barshes NR, Lin PH, Lai WS, Kougias P. Risk factors and impact of proximal fixation on acute and chronic renal dysfunction after endovascular aortic aneurysm repair using glomerular filtration rate criteria. Ann Vasc Surg. 2013;27(1):16–22.

30. Wesselink EM, Kappen TH, Torn HM, Slooter AJC, van Klei WA. Intraoperative hypotension and the risk of postoperative adverse outcomes: a systematic review. Br J Anaesth. 2018;121(4):706–21.

31. Vernooij LM, van Klei WA, Machina M, Pasma W, Beattie WS, Peelen LM. Different methods of modelling intraoperative hypotension and their association with postoperative complications in patients undergoing non-cardiac surgery. Br J Anaesth. 2018;120(5):1080–9.

32. Walsh M, Kurz A, Turan A, Rodseth RN, Cywinski J, Thabane L, et al. Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery. Anesthesiology. 2013;119(3):507–15.

33. Yue J-N, Luo Z, Guo D-Q, Xu X, Chen B, Jiang J-H, et al. Evaluation of acute kidney injury as defined by the risk, injury, failure, loss, and end-stage criteria in critically ill patients undergoing abdominal aortic aneurysm repair. Chin Med J (Engl).

2013;126(3):431–6.

34. Brinkman R, HayGlass KT, Mutch WAC, Funk DJ. Acute kidney injury in patients undergoing open abdominal aortic aneurysm repair: A pilot observational trial. J Cardiothorac Vasc Anesth. 2015;29(5):1212–9.

35. Davidovic LB, Maksic M, Koncar I, Ilic N, Dragas M, Fatic N, et al. Open repair of AAA in a high volume center. World J Surg. 2017;41(3):884–91.

36. van Waes JAR, van Klei WA, Wijeysundera DN, van Wolfswinkel L, Lindsay TF, Beattie WS. Association between intraoperative hypotension and myocardial injury after vascular surgery. Anesthesiology. 2015;124(1):35–44.

37. Bijker JB, van Klei WA, Vergouwe Y, Eleveld DJ, van Wolfswinkel L, Moons KGM, et al. Intraoperative hypotension and 1-year mortality after noncardiac surgery. Anesthesiology. 2009;111(6):1217–26.

38. Sun LY, Wijeysundera DN, Tait GA, Beattie WS. Association of intraoperative hypotension with acute kidney injury after elective non-cardiac surgery. Anesthesiology. 2015;123(3):515–23.

39. Monk TG, Saini V, Weldon BC, Sigl JC. Anesthetic management and one-year mortality after noncardiac surgery. Anesth Analg. 2005;100(1):4–10.

40. Goren O, Matot I. Perioperative acute kidney injury. Br J Anaesth. 2015;115(2, SI):3–14.

41. Sabaté S, Mases A, Guilera N, Canet J, Castillo J, Orrego C, et al. Incidence and predictors of major perioperative adverse cardiac and cerebrovascular events in non-cardiac surgery. Br J Anaesth. 2011;107(6):879–90.

42. Kheterpal S, Rosenberg AL, Shanks AM, Tremper KK, Englesbe MJ, Campbell DA, et al. Preoperative and intraoperative predictors of cardiac adverse events after general, vascular, and urological surgery. Anesthesiology. 2009;110(1):58–66.

43. Mascha EJ, Yang D, Weiss S, Sessler DI. Intraoperative mean arterial pressure variability

and 30-day mortality in patients having noncardiac surgery. Anesthesiology. 2015;123(1):79–91.

44. Salmasi V, Maheshwari K, Yang D, Mascha EJ, Singh A, Sessler DI, et al. Thresholds , and acute kidney and myocardial injury after noncardiac surgery A retrospective cohort analysis. Anesthesiology. 2017;126(1):47–65.

45. Macedo E, Castro I, Yu L, Abdulkader RRC, Vieira Jr. JM. Impact of mild acute kidney injury (AKI) on outcome after open repair of aortic aneurysms. Ren Fail. 2008;30(3):287–96.

46. Garg AX, Devereaux PJ, Hill A, Sood M, Aggarwal B, Dubois L, et al. Oral curcumin in elective abdominal aortic aneurysm repair: A multicentre randomized controlled trial. Can Med Assoc J. 2018;190(43):E1273–80.

47. Ellenberger C, Schweizer A, Diaper J, Kalangos A, Murith N, Katchatourian G, et al. Incidence, risk factors and prognosis of changes in serum creatinine early after aortic abdominal surgery. Intensive Care Med. 2006;32:1808-1816.

48. Kheterpal S, Tremper KK, Heung M, Rosenberg AL, Englesbe M, Shanks AM, et al. Development and validation of an acute kidney injury risk index for patients undergoing general surgery: Results from a national data set. Anesthesiology. 2009;110(3):505–15.

49. Hobson C, Lysak N, Huber M, Scali S, Bihorac A. Epidemiology, outcomes, and management of acute kidney injury in the vascular surgery patient. J Vasc Surg. 2018;68(3):916–28.

50. SAS Institute Inc. SAS/STAT® 14.3 User's Guide. 2017;Cary, NC:SAS Institute Inc.

51. Hosmer D, Lemeshow S. Goodness of fit tests for the multiple logistic regression model. Commun Stat. 1980;A(10):1043–69.

52. Brabant SM, Bertrand M, Eyraud D, Darmon P-L, Coriat P. The hemodynamic effects of anesthetic induction in vascular surgical patients chronically treated with angiotensin II receptor antagonists. Anesth Analg. 1999;89(6):1388.

53. Vaquero Roncero LM, Sánchez Poveda D, Valdunciel García JJ, Sánchez Barrado ME, Calvo Vecino JM. Perioperative use of angiotensin-converting-enzyme inhibitors and angiotensin receptor antagonists. J Clin Anesth. 2017;40:91–8.

Chapter 4

4 Systematic review and meta-analysis of preventive strategies for acute kidney injury in patients undergoing elective abdominal aortic aneurysm repair

4.1 Introduction

Acute kidney injury (AKI) is a frequent complication after abdominal aortic aneurysm (AAA) repair.[1] Proposed mechanisms of AKI following AAA repair include renal ischemia due to aortic cross clamping in open repair, use of nephrotoxic medications including contrast in endovascular aortic aneurysm repair (EVAR), and atheroembolization to the kidney during either procedure.[1,2] Patients who demonstrate post-operative AKI have a high risk of morbidity, mortality, a long length of hospital stay, and high healthcare costs; some patients never recover and are left with new chronic kidney disease or end-stage kidney disease.[1,3–6] AKI incidence after EVAR ranges from 1% to 19% ; [1,7–9] while AKI incidence after open aortic aneurysm repair ranges from 2% to 29.9%.[5,7,10–19] The incidence, rate and severity of AKI across reported studies may be underestimated.[20,21]

Effective methods to prevent postoperative AKI among patients undergoing elective AAA repair have not been well established. Previous systematic reviews have examined AKI in AAA repair patients but have focused on only one population of open or endovascular repair, or on all vascular surgery patients and were limited by varying definitions of AKI across included studies.[15,22,23] None of the currently available systematic reviews has completed a review of all preventive interventions but have focused on a single intervention of interest such as mannitol.[24]. This review was conducted to identify preventive interventions for AKI among elective AAA repair patients in RCTs.

4.2 Methods

Protocol and Registration

The protocol for this review is published on PROSPERO. The registration ID is CRD42018100310 and is available at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=100310.

Information Sources and Search

We searched Medline OVID (1966 - 2018), EMBASE (1947 – 2018), CINAHL (1961 – 2018), Web of Science (1945 – 2018), Scopus (1966 - 2018), and The Cochrane Library (1996 – 2018) for all relevant articles. The search strategy was developed with the assistance of an expert librarian (J.C.) and included terms relating to or describing elective AAA repair and AKI (Appendix A1). The search terms were adapted for use with each database. ProQuest Dissertations and Theses Global, Clinicaltrials.gov and ICTRP – WHO were searched for grey literature relevant to the review. Reference lists and all bibliographic data of retrieved articles were screened for relevant studies. Two reviewers (M.F. and M.M.) independently screened the results and those considered potentially relevant by any reviewer were retrieved for full-text review.

Study Selection and Eligibility

Databases were searched for any published English manuscripts of relevant studies available on the search date (October 19th, 2018). Randomized controlled trials (RCTs) involving adult patients undergoing elective abdominal aortic aneurysm repair by the open and/or the endovascular procedure (juxtarenal, suprarenal, pararenal and infrarenal) were included. Studies

involving ruptured aneurysms or thoracoabdominal aneurysm were excluded, as were studies involving a mixed patient population for example including patients treated for aortic occlusive disease. The review focused on preventive interventions for AKI administered anytime pre-, intra- or post-operatively.

Comparators of interventions were another intervention, placebo or standard care. Outcomes included in the review were incidence of AKI measured by serum creatinine (SCr), creatinine clearance (CrCl) or using the Kidney Disease: Improving Global Outcomes (KDIGO), Risk, Injury, Failure, Loss, End-Stage Kidney Disease (RIFLE) or Acute Kidney Injury Network (AKIN) criteria, incidence of renal replacement therapy and mortality.[25–27] Any discrepancy in study inclusion was resolved by consensus or appeal to a third reviewer (L.D.).

Data Extraction

The data extraction was carried out by two independent reviewers (M.F. and M.M.) using a standardized form. The eligibility of the study was recorded including the inclusion and exclusion criteria. The methods of the study recorded by the reviewers included the sample size, the study design, the study location, and the follow up. Patient information recorded by the reviewers included age, sex, baseline characteristics and comorbidities such as previous RRT. The interventions and the related information from before and after treatment, and intervention side effects, were also collected. The comparability of groups, confounding factors and methods of adjustment, multiple effect estimates (both adjusted and unadjusted) and sources of funding were collected. The outcome information collected included the number of events, the primary outcomes, the cost-data utilities and the secondary outcomes. The extracted data were combined and presented in a table of study characteristics (Table 4-1).

Risk of Bias

The studies included in this systematic review were limited to randomized controlled trials (RCTs). The RCTs were assessed using the Cochrane collaboration risk of bias tool (CCRBT).[28] CCRBT assesses the quality of an RCT using 6 classifications: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other potential threats to validity. The classifications were assessed as low, high and unclear risks of bias. If all classifications were assessed as having low risk of bias, the overall study was classified as having low risk of bias. If two classifications were assessed as high or unclear risk of bias, the overall study was classified as having a moderate risk of bias. If more than 3 classifications were assessed as high or unclear risk of bias, the study was classified as having high risk of bias (Table 4-3). Study quality was assessed by two independent reviewers. Between-study risk of bias was not assessed for publication bias due to the small number of studies available for meta-analysis.[29–31]

Data Analysis

Where we could, we pooled studies using techniques that accounted for within- and between-study heterogeneity by using a random effects model using RevMan (*Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.*). Heterogeneity of treatment effects between studies were assessed with the Cochrane Q and the I^2 statistics.[32]

4.3 Results

Retrieval of Studies

Our search resulted in 5428 citations retrieved from the following databases: Ovid Medline (1066), Ovid EMBASE (2604), Scopus (1107), Web of Science (367), CINAHL (80), The Cochrane Library (176), Dissertations and Theses Global, clinicaltrials.gov and ICTRP-WHO (28). A total of 1856 duplicate articles were removed from review. A total of 209 articles were removed as they were not available in English. The reference lists of relevant articles were reviewed for additional material (Figure 4-I). A total of 27 studies were identified for full-text screening. A total of 17 studies (1443 number of patients) met eligibility criteria for inclusion in this review (Table 4-1).

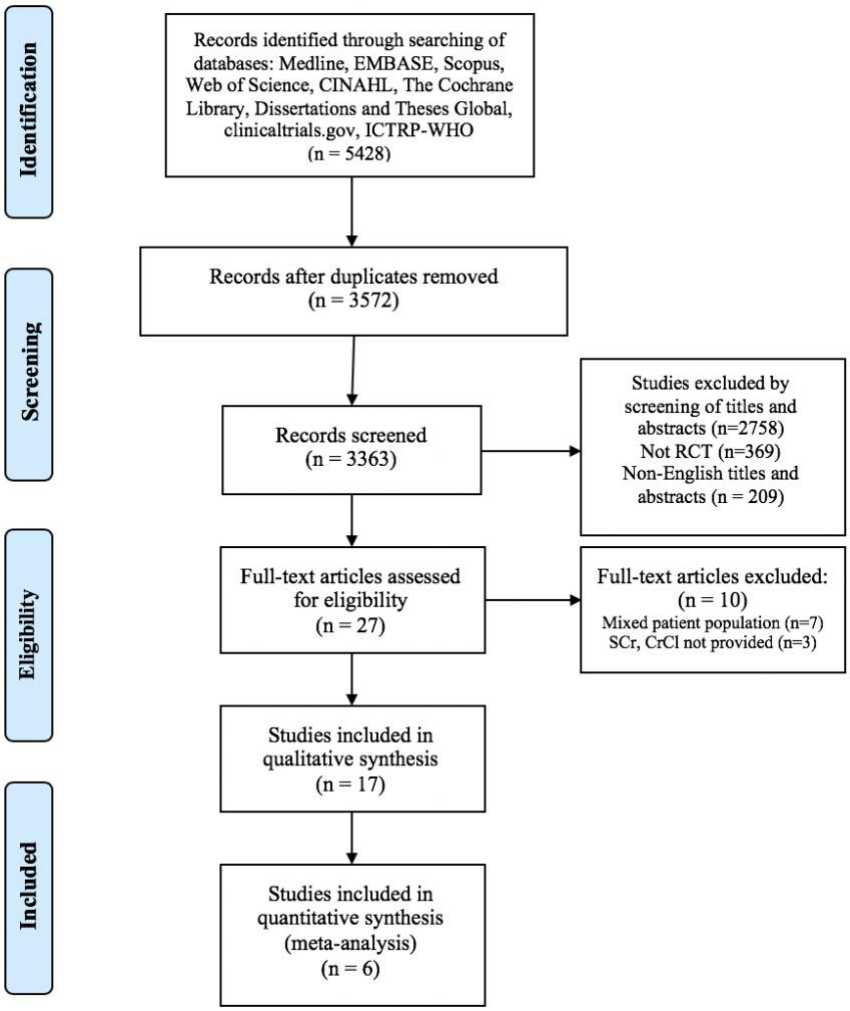

Figure 4-1 PRISMA flow chart of study selection

Table 4-1 Characteristics of included studies

Source	Intervention	Country of Origin	Number of patients	EVAR/Open (%)	Mean patient age, years	Male (%)
Turner et al, 2007[33]	Methylprednisolone	UK	18	100% Open	70	NA
Garg et al, 2018[34]	Curcumin	Canada	606	53% EVAR/47% Open	76	83%
Wijnen et al, 2002[35]	Multi-antioxidant supplementation	Netherlands	42	100% Open	69	93%
Lau et al, 2001[36]	Extraperitoneal vs Transperitoneal Approach	Ireland	20	100% Open	72	95%
de Almeida Mendes et al, 2017[37]	Carbon Dioxide Contrast Medium	Brazil	36	100% EVAR	71	83%
Saratzis et al, 2018[38]	Sodium Bicarbonate and Hydration	UK	58	100% EVAR	75	79%
Bonazzi et al, 2002[39]	Haemodynamic optimization	Italy	100	100% Open	68	100%

Mahmood et al, 2007[40]	Hydroxyethyl starch vs gelatine	UK	62	100% Open	72	81%
Kalimeris et al, 2014[41]	Mannitol	Greece	86	100% EVAR	72	98%
Moore et al, 2006[42]	N-acetylcysteine	UK	20	100% EVAR	72	100%
Mitaka et al, 2008[43]	human Atrial Natriuretic Peptide	Japan	40	100% Open	71	88%
Mouton et al, 2015[44]	Remote ischemic preconditioning (RIPC)	UK	69	65% EVAR/35% Open	72	NA
Murphey et al, 2014[45]	Remote ischemic preconditioning (RIPC)	Ireland	62	100% Open	72	86%
Walsh et al, 2009[46]	Remote ischemic preconditioning (RIPC)	UK	40	100% EVAR	75	62%
Walsh et al, 2010[47]	Remote ischemic preconditioning (RIPC)	UK	40	100% Open	74	85%
Ali et al, 2007[48]	Remote ischemic preconditioning (RIPC)	UK	82	100% Open	75	93%

Li et al, 2013[49]	Remote ischemic preconditioning (RIPC)	China	62	100% Open	65	90%

Abbreviations: NA = Not Available, EVAR = Endovascular Aneurysm Repair, RIPC= Remote Ischemic Preconditioning

Study Characteristics

Of the seventeen studies, eleven analyzed: methylprednisolone[33], curcumin[34], a combination of antioxidant supplements[35], extraperitoneal vs. transperitoneal approach[36], carbon dioxide contrast medium[37], sodium bicarbonate[38], haemodynamic monitoring[39], hydroxyethyl starch[40], mannitol[41], N-acetylcysteine[42], and human atrial natriuretic peptide[43] (Table 4-2). The other six analyzed the effects of remote ischemic preconditioning[44–49] (Table 4-2). The studies were conducted in the UK (n=8), Canada (n=1), the Netherlands (n=1), Ireland, (n=2), Brazil (n=1), Italy (n=1), China (n=1), Japan (n=1) and Greece (n=1). The sample size of the studies ranged from 18 to 606 patients. Three studies had samples of 20 patients or less, five studies had between 21 and 50 patients, eight studies had between 51 and 100 patients and one study had 606 patients. Of the 17 studies, 15 were single-centre studies. The other two were multi-centre studies with two and ten centres respectively.[34,38] None of the studies was funded by industry sponsors. The patients in all the studies underwent either an open or endovascular (EVAR) elective repair. Of the seventeen studies, ten trials involved patients undergoing entirely open repair (59%), five had entirely EVAR (29%) and two had a mix of open and EVAR repair (12%) (Table 4-1). Definitions of AKI, AKI stages and renal replacement therapy (RRT) initiation were different across studies (Table 4-2).

Table 4-2 Intervention and renal outcome details of included studies

Source	Intervention	Control	Renal Outcome	Renal Results
Turner et al, 2007[33]	Methylprednisolone 10mg/kg prepared in 500mL 5% dextrose	500mL 5% dextrose	SCr	Increased SCr for intervention group (*P*<0.001)
Garg et al, 2018[34]	Curcumin p.o., 2000mg x 8 doses	Placebo	AKI, SCr	Higher risk of AKI (17% vs 10%) for intervention group (*P*=0.01), no significant between-group difference in SCr rise (1 vs 1umol/L) (*P*=0.2)
Wijnen et al, 2002[35]	Multi-antioxidant supplementation: Vitamin E 200mg qd x 5 doses, Vitamin C 2000mg, Allopurinol 300mg p.o. day before surgery and 300mg i.v. before operation, N-Acetylcysteine 150mg/kg before surgery and 200mg/kg i.v 12 hrs, Mannitol i.v. 10% 500mg/mL 12hrs at start of surgery	Standard therapy	CrCl, SCr	24 hr CrCl higher on day 2 for intervention group (*P*=0.047), No significant difference in SCr (*P*>0.05)

Lau et al, 2001[36]	Extraperitoneal approach	Transperitoneal approach	SCr	SCr significantly lower on day 1 (P<0.01) and 2 (P<0.05) for intervention group
de Almeida Mendes et al, 2017[37]	Carbon Dioxide	Iodine Contrast Medium	CrCl, AKI	No significant difference in CrCl (P=0.80) No cases of AKI
Saratzis et al, 2018[38]	1mmol/kg or 1mL/kg of an 8.4% Sodium Bicarbonate solution and Hydration	Standard Hydration	AKI	Risk Ratio=0.2 (95% CI: 0.1 – 0.8)
Bonazzi et al, 2002[39]	Haemodynamic optimization	Conventional treatment	Renal failure, RRT	No cases of renal failure, no significant difference in RRT (P>0.05)
Mahmood et al, 2007[40]	Hydroxyethyl starch – 6% HES with a mean molecular weight of 200 kDa and a degree of hydroxyethyl substitution of 0.62 OR 6% HES with a mean molecular weight of 130 kDa and a degree of hydroxyethyl substitution of 0.4	4% Gelatine	SCr	SCr was significantly lower on days 1 (P=0.02), 2 (P=0.045) and 5 (P=0.045) using both HES solutions

Kalimeris et al, 2014[41]	20% Mannitol 0.5 g/kg over 15 minutes	Standard Therapy	Renal dysfunction, SCr	No significant difference in renal dysfunction (*P*=0.30), SCr lower at 24 hours: mannitol 1.07+/- 0.26 vs. control 1.20 +/- 0.30 (*P*<0.05)
Moore et al, 2006[42]	N-acetylcysteine 600mg b.i.d orally x 4 doses	Standard fluid hydration	AKI, SCr	No cases of AKI, No significant differences in SCr (*P*>0.05)
Mitaka et al, 2008[43]	hANP (0.01–0.05 ug/kg/min) infusion prior to cross clamp for 48 hours postoperatively	Placebo	SCr, CrCl	SCr significantly lower (*P*<0.05)and CrCl significantly higher (*P*<0.05) in intervention group
Mouton et al, 2015[44]	Remote ischemic preconditioning (RIPC) – 3 cycles of upper limb 5 min ischemia/5 min reperfusion	Sham cuff	AKI	AKIN1: 27% vs 20%, AKIN2: 21% vs 9%, AKIN3: 0% vs 6%
Murphey et al, 2014[45]	Remote ischemic preconditioning (RIPC) – 3 cycles of upper limb	Sham cuff	AKI, SCr	No significant differences in SCr (*P*>0.05), AKI (AKIN) 55% vs 36%

	5 min ischemia/5 min reperfusion			(*P*=0.12), RRT 23% vs 0% (*P*=0.01)
Walsh et al, 2009[46]	Remote ischemic preconditioning (RIPC) – 2 sequential periods of lower limb ischemia and reperfusion	Conventional treatment	Renal failure, renal impairment, SCr	No significant difference in renal impairment 22% vs 9% (*P*=0.29), SCr (*P*=0.88), No cases of renal failure
Walsh et al, 2010[47]	Remote ischemic preconditioning (RIPC) – 2 cycles of common iliac vessel cross-clamping 10 min ischemia/10 min reperfusion	Conventional treatment	Renal failure, renal impairment SCr	No significant difference in SCr (*P*>0.05), renal failure 18% vs 5.5% (*P*=0.28) or renal impairment 50% vs 56% (*P*=0.73)
Ali et al, 2007[48]	Remote ischemic preconditioning (RIPC) - 2 cycles of common iliac vessel cross-clamping 10 min ischemia/10 min reperfusion	Conventional treatment	AKI, SCr	AKI 7% vs 30% (*P*=0.009), $OR_{adjusted}$= 0.2 95% CI: 0.1-0.7, (*P*=0.01)
Li et al, 2013[49]	Remote ischemic preconditioning (RIPC) – 3 cycles of upper limb 5 min ischemia/5 min reperfusion	Sham cuff	Renal failure, RRT	No cases of renal failure or RRT

Abbreviations: SCr = Serum Creatinine, AKI = Acute Kidney Injury, CrCl = Creatinine Clearance, RRT = Renal Replacement Therapy, HES = Hydroxyethyl starch, hANP = human Atrial Natriuretic Peptide, RIPC = Remote Ischemic Preconditioning, Renal results compared between groups (interventions vs controls)

Quality

Seven of the studies were at high risk of bias, four were at moderate risk of bias and six were at low risk of bias (Table 4-3). Three studies (17%) had 0% of patient attrition.[43,45,49] Two studies (12%) had less than 5% of patient attrition [34,44] and four studies (24%) had greater than 5% of patient attrition [33,38,40,41]. The remaining eight studies (47%) did not explicitly discuss attrition in terms of loss to follow up or exclusion.[35–37,39,42,46–48] The assessment of renal function differed across studies, some reporting as soon as 1, 2, 6, 24 and 48 hours[33] following and others on days 1, 3 and 7[48].

Table 4-3 Risk of bias of included studies

Source	Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data	Selective Outcome Reporting	Other Potential Threats to Validity	Overall
Turner et al, 2007[33]	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Garg et al, 2018[34]	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Wijnen et al, 2002[35]	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	HIGH
Lau et al, 2001[36]	UNCLEAR	UNCLEAR	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	HIGH

de Almeida Mendes et al, 2017[37]	LOW	HIGH	HIGH	UNCLEAR	UNCLEAR	LOW	HIGH
Saratzis et al, 2018[38]	LOW	HIGH	HIGH	HIGH	LOW	LOW	HIGH
Bonazzi et al, 2002[39]	LOW	LOW	HIGH	UNCLEAR	LOW	LOW	MODE-RATE
Mahmood et al, 2007[40]	LOW	LOW	HIGH	LOW	HIGH	LOW	MODE-RATE
Kalimeris et al, 2014[41]	LOW	LOW	HIGH	HIGH	UNCLEAR	LOW	HIGH
Moore et al, 2006[42]	LOW	HIGH	HIGH	UNCLEAR	UNCLEAR	LOW	HIGH
Mitaka et al, 2008[43]	HIGH	HIGH	HIGH	LOW	UNCLEAR	LOW	HIGH
Mouton et al, 2015[44]	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Murphey et al, 2014[45]	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Walsh et al, 2009[46]	LOW	LOW	HIGH	UNCLEAR	LOW	LOW	MODE-RATE
Walsh et al, 2010[47]	LOW	LOW	HIGH	UNCLEAR	LOW	LOW	MODE-RATE

Ali et al, 2007[48]	LOW	LOW	LOW	UNCLEAR	LOW	LOW	LOW
Li et al, 2013[49]	LOW	LOW	LOW	UNCLEAR	LOW	LOW	LOW

AKI

The incidence of AKI was reported as a dichotomous outcome in four studies, as a continuous outcome in five studies and as both dichotomous and continuous in eight studies. The reported renal outcomes were different across all studies with five studies reporting renal function in terms of SCr or CrCl, five studies reporting renal failure/impairment/dysfunction and seven studies reporting AKI using various definitions. Mannitol, a composite of antioxidant supplements, sodium bicarbonate, an open extraperitoneal approach, hANP and HES with crystalloid have been shown to reduce AKI or improve renal function (Table 4-2).[35,36,38,40,41,43] Serum creatinine was significantly lower at 24 hours between mannitol and control groups (n=86, $P<0.05$), with no significant difference between groups in renal dysfunction ($P=0.30$). The multi-antioxidant supplements had significantly higher CrCl on postoperative day 2 compared to the control group (n=42, $P=0.047$). The patients that received sodium bicarbonate and standard hydration had 0.21 times the risk of AKI, compared to patients that received standard hydration alone (n=58, relative risk = 0.2, 95% CI 0.1 – 0.9). Serum creatinine was significantly lower on postoperative day 1 and 2 in patients that had an extraperitoneal approach compared to those that had a transperitoneal approach (n=20, $P<0.01$, $P<0.05$). Mean SCr concentrations were significantly lower on postoperative days 1,2 and 3 among the hANP group compared to placebo (n=40, $P<0.05$) and CrCl was significantly higher in the hANP group compared to the placebo group ($P<0.05$). The HES solutions had significantly lower SCr on days

1, 2 and 5 postoperatively, compared to gelatine (n=62, *P*=0.02, *P*=0.045, *P*=0.045). These results indicate a possible protective effect for AKI.

The results for all relevant interventions are presented in Table 4-2. [33,34,37,39,42–49] Methylprednisolone, curcumin, carbon dioxide contrast medium, haemodynamic monitoring, and N-acetylcysteine were not associated with a reduction in AKI or improvement in renal function (Table 4-2).[33,34,37,39,42] Methylprednisolone was found to increase SCr (n=18, *P*<0.001), indicating an adverse effect on postoperative renal function.[33] Curcumin was found to have a higher incidence of AKI in the intervention group (17% vs. 10%, *P*=0.01) and no significant difference between groups regarding the perioperative change in SCr (n=606, *P*=0.2).[34] Carbon dioxide contrast medium, haemodynamic monitoring, and N-acetylcysteine did not indicate a statistically significant difference in renal function between groups.[37,39,42]

RIPC is the remote application, for example a pressure cuff applied to an upper or lower limb, for a period of ischemia followed by a period of reperfusion in an effort to provide systemic protection against cellular injury during the ischemic episode, in this case AAA repair. The 6 studies of 355 patients investigating RIPC were pooled in a meta-analysis (Figure 4-2).[44–49] The results show no statistically significant difference between RIPC and standard treatment in reducing the incidence of postoperative AKI (OR 1.2, 95% CI 0.4, 3.9). This should be interpreted with caution due to considerable statistical heterogeneity (Q=9.96, df=3, I^2=70%) (Figure 4-2).[44–49]

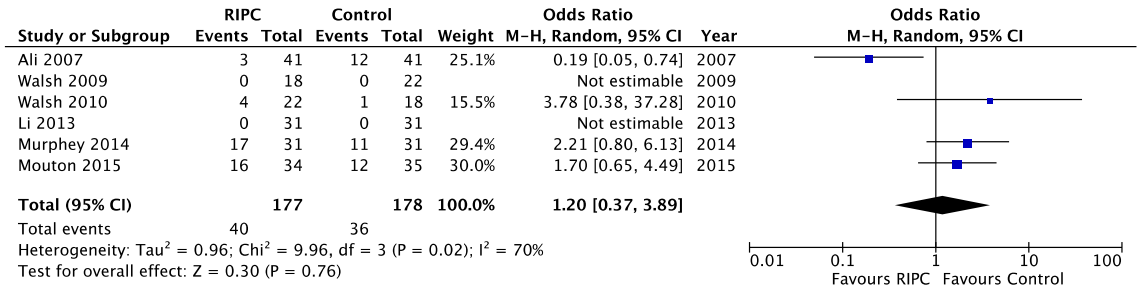

Figure 4-2 Forest plot comparing remote ischemic preconditioning with control on the effect on acute kidney injury

Renal Replacement Therapy

The incidence of RRT was reported in 13 studies consisting of 1385 patients.[34,37,42,44–49] None of the studies reported predefined criteria for initiation of RRT among patients. No clear benefit was found supporting any intervention in any study for reducing the incidence of RRT among elective AAA repair patients and none of the trials was adequately powered to study this outcome. Murphey et al reported a significantly greater number of patients that required RRT among the RIPC intervention group following open elective AAA repair compared to the control group (7 vs 0, *P*=0.01).[45] Of the seven patients requiring RRT, six required a secondary surgical intervention which was associated with the initiation of RRT. They postulate this finding may be due to chance as the study was not powered to detect a difference for this outcome.[45]

Mortality

Mortality was reported in 16 of 17 studies comprised of 1345 patients.[33–37,39–49] Fifteen of the sixteen studies considered death as a single end point and one study included death as a composite end point.[34] No clear benefit was found supporting any intervention for reducing mortality and none of the trials was adequately powered to study this outcome.

4.4 Discussion

This systematic review demonstrates the paucity of well-designed RCTs evaluating preventive interventions for AKI in elective AAA repair patients. The trials generally were small, single-centre, clinically and methodologically diverse resulting in statistical heterogeneity, of low methodological quality and underpowered to detect differences in AKI, mortality or RRT. The parameters used to define AKI were primarily in serum creatinine or creatinine clearance with few defining AKI using the RIFLE or AKIN criteria.[25,26] Only one of the studies used the recently described KDIGO criteria.[38] Clinically important endpoints of mortality or RRT were not considered primary endpoints in most of the studies, as the trials did not have adequate statistical power to meaningfully look at this outcome. Analysis of the trials did identify a few interventions that may possibly be associated with beneficial protective effects for the prevention of AKI.

Possible protective effects were identified for mannitol, a composite of antioxidant supplements, sodium bicarbonate, an open extraperitoneal approach, hANP and HES combined with crystalloid for the prevention of AKI postoperatively. Although HES has been shown to be possibly beneficial in one trial included in this review it has largely gone out of favour in the clinical community. This is based on contraindicating evidence found in larger, well powered studies involving critically ill patients which have found a negative effect of starch solutions on mortality and RRT.[50,51] Sodium bicarbonate has also been shown to be possibly beneficial in one trial included in this review, however, there may be a lack of enthusiasm for this intervention given large RCTs that demonstrated no benefit for sodium bicarbonate for the prevention of death, RRT, or contrast-associated AKI among patients undergoing angiography.[52] Mannitol, the composite of anti-oxidant supplements, an open extraperitoneal approach and hANP show

promise for future RCT investigation. The results presented were based on small, low quality, high risk of bias RCTs and the effects of these interventions should be further investigated using large, high quality, multi-centre RCTs.

No evidence of effect was found for the other interventions; however, the majority of studies were underpowered to detect a difference. The curcumin RCT was the largest trial with 606 patients included in the analysis.[34] AKI was found to be significantly higher in the group receiving curcumin (P=0.01), indicating the importance of investigating herbal supplements and the associated adverse effects that often go unknown or unpublished.[34]

The meta-analysis of RCTs examining the RIPC intervention indicates no significant difference between RIPC and control. The trials were single-centre, small in size (40 to 82 patients) and of low to moderate risk of bias. Meta-analysis of these trials was limited by statistical heterogeneity which was mainly due to a single study showing benefit for RIPC. In examining the study's clinical characteristics, we cannot identify an obvious reason for the discrepant findings when compared to the other studies which were all negative. We suspect that RIPC is not effective in the prevention of AKI however future trials should be well powered, use a defined protocol and use appropriate definitions of AKI.

Future research must consider a variety of factors when designing and conducting RCTs in this setting. Significant risk factors associated with AKI have been studied indicating that the development of AKI may be multifactorial. The preventive interventions related to these risk factors could be administered at once or in succession to study multiple interventions. Future trials should be designed according to how well powered they are to detect certain endpoints as previously suggested in a systematic review in the cardiac surgery setting.[53] Surrogate endpoints such as AKI defined by SCr using KDIGO criteria or changes in relevant biomarkers should be

used in smaller trials in Phase I or II of development. Clinically relevant and critically important hard endpoints such as mortality, RRT, length of hospitalization and long-term outcomes including CKD or mortality should be used in well powered trials in phase III or IV of development. Studies should be designed to include patients with CKD, as CKD patients have the highest absolute risk of peri-operative AKI excluding those with end-stage renal disease (ESRD) as AKI is less relevant.[20,54]

Our review has many strengths beginning with a comprehensive search of the relevant literature of over 5000 studies. The screening, selection, eligibility criteria assessment and data extraction were completed independently by two reviewers (MF and MM) to minimize bias. We also limited our inclusion to RCT in order to focus on potentially more impactful studies.

A limitation of this review is the exclusion of non-English studies from consideration. This resulted in exclusion of 209 studies of the 5428 screened. Some studies have suggested that exclusion of non-English studies do not bias the effect estimates of meta-analyses.[55,56] The trials that were identified were generally small, single centre, of poor methodological quality and significantly underpowered. The definitions of AKI were highly variable, and only one of which used the recently identified KDIGO criteria for AKI definition.[27] Future trials should follow the KDIGO criteria for defining AKI.

4.5 Conclusion

A small number of relevant studies were found, and most were small, single-centre, of low methodological quality and underpowered to detect differences in AKI, mortality and RRT. The possible beneficial effects of mannitol, a composite of antioxidant supplements, an open

extraperitoneal approach and hANP demonstrates the need for investigation into these strategies in future RCTs. The largest study of 606 patients receiving curcumin preoperatively found higher rates of AKI in patients receiving the supplement thus highlighting the need to study herbal supplements carefully to avoid doing harm. Among patients undergoing elective AAA repair, the lack of available literature for preventive strategies for AKI highlight the need for large, high quality, multi-centre studies to identify interventions for reducing the incidence of postoperative AKI, mortality and RRT.

4.6 References

1. Saratzis AN, Goodyear S, Sur H, Saedon M, Imray C, Mahmood A. Acute kidney injury after endovascular repair of abdominal aortic aneurysm. J Endovasc Ther. 2013;20(3):315–30.

2. Dariane C, Coscas R, Boulitrop C, Javerliat I, Vilaine E, Goeau-Brissonniere O, et al. Acute kidney injury after open repair of intact abdominal aortic aneurysms. Ann Vasc Surg. 2017;39:294–300.

3. Hudorović N, Lovričević I, Brkić P, Ahel Z, Vičić-Hudorović V. Renal replacement therapies after abdominal aortic aneurysm repair - A review. Acta Clin Croat. 2011;50(3):403–14.

4. Kazmers A, Jacobs L, Perkins A. The impact of complications after vascular surgery in Veterans Affairs Medical Centers. J Surg Res. 1997;67(1):62–6.

5. Johnston KW. Multicenter prospective study of nonruptured abdominal aortic aneurysm. Part II. Variables predicting morbidity and mortality. J Vasc Surg. 1989;9(3):437–47.

6. Chertow GM, Burdick E, Honour M, Bonventre J V., Bates DW. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. J Am Soc Nephrol. 2005;16(11):3365–70.

7. Wald R, Waikar SS, Liangos O, Pereira BJG, Chertow GM, Jaber BL. Acute renal failure after endovascular vs open repair of abdominal aortic aneurysm. J Vasc Surg. 2006;43(3):466.

8. Abraham CZ, Chuter TAM, Reilly LM, Okuhn SP, Pethan LK, Kerlan RB, et al. Abdominal aortic aneurysm repair with the Zenith stent graft: Short to midterm results. J Vasc Surg. 2002;36(2):217–25.

9. Prinssen M, Verhoeven ELG, Buth J, Cuypers PWM, van Sambeek MRHM, Balm R, et al. A randomized trial comparing conventional and endovascular repair of abdominal aortic aneurysms. N Engl J Med. 2004;351(16):1607–18.

10. Greenberg RK, Chuter TAM, Lawrence-Brown M, Haulon S, Nolte L. Analysis of renal function after aneurysm repair with a device using suprarenal fixation (Zenith AAA Endovascular Graft) in contrast to open surgical repair. J Vasc Surg. 2004;39(6):1219–28.

11. Adriaensen MEAPM, Bosch JL, Halpern EF, Myriam Hunink MG, Gazelle GS. Elective endovascular versus open surgical repair of abdominal aortic aneurysms: Systematic review of short-term results. Radiology. 2007;224(3):739–47.

12. Chen JC, Hildebrand HD, Salvian AJ, Taylor DC, Strandberg S, Myckatyn TM, et al. Predictors of death in nonruptured and ruptured abdominal aortic aneurysms. J Vasc Surg. 1996;24(4):613–4.

13. Hertzer NR, Mascha EJ, Karafa MT, O'Hara PJ, Krajewski LP, Beven EG. Open infrarenal abdominal aortic aneurysm repair: The Cleveland Clinic experience from 1989 to 1998. J Vasc Surg. 2002;35(6):1145–54.

14. Hua HT, Cambria RP, Chuang SK, Stoner MC, Kwolek CJ, Rowell KS, et al. Early outcomes of endovascular versus open abdominal aortic aneurysm repair in the National Surgical Quality Improvement Program-Private Sector (NSQIP-PS). J Vasc Surg. 2005;41(3):382–9.

15. Dariane C, Coscas RR, Boulitrop C, Javerliat I, Vilaine E, Goeau-Brissonniere O, et al. Acute kidney injury after open repair of intact abdominal aortic aneurysms. Ann Vasc Surg. 2017;39(November 2016):294–300.

16. Shahverdyan R, Majd MP, Thul R, Braun N, Gawenda M, Brunkwall J, et al. F-EVAR does not impair renal function more than open surgery for juxtarenal aortic aneurysms: Single centre results. Eur J Vasc Endovasc Surg. 2015;50(4):432–41.

17. Castagno C, Varetto G, Quaglino S, Frola E, Scozzari G, Bert F, et al. Acute kidney injury after open and endovascular elective repair for infrarenal abdominal aortic aneurysms. J Vasc Surg. 2016;64(4):928+.

18. Tang Y, Chen J, Huang K, Luo D, Liang P, Feng M, et al. The incidence, risk factors and in-hospital mortality of acute kidney injury in patients after abdominal aortic aneurysm repair surgery. BMC Nephrol. 2017;18(1):184.

19. Surowiec SM, Davies MG, Fegley AJ, Tanski WJ, Pamoukian VN, Sternbach Y, et al. Relationship of proximal fixation to postoperative renal dysfunction in patients with

normal serum creatinine concentration. J Vasc Surg. 2004;39(4):804–10.

20. Zabrocki L, Marquardt F, Albrecht K, Herget-Rosenthal S. Acute kidney injury after abdominal aortic aneurysm repair: current epidemiology and potential prevention. Int Urol Nephrol. 2018;50(2):331–7.

21. Saratzis A, Melas N, Mahmood A, Sarafidis P. Incidence of acute kidney injury (AKI) after endovascular abdominal aortic aneurysm repair (EVAR) and impact on outcome. Eur J Vasc Endovasc Surg. 2015;49(5):534–40.

22. Saratzis AN, Goodyear S, Sur H, Saedon M, Imray C, Mahmood A. Acute kidney injury after endovascular repair of abdominal aortic aneurysm. J Endovasc Ther. 2013;20(3):315–30.

23. Zacharias M, Mugawar M, Herbison GP, Walker RJ, Hovhannisyan K, Sivalingam P, et al. Interventions for protecting renal function in the perioperative period. Cochrane Database Syst Rev. 2013;(9).

24. Waskowski J, Pfortmueller CA, Erdoes G, Buehlmann R, Messmer AS, Luedi MM, et al. Mannitol for the prevention of peri-operative acute kidney injury: A systematic review. Eur J Vasc Endovasc Surg. 2019, article in press.

25. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure: definition, outcome measures, animal models, fluid therapy and information technology needs. Crit Care. 2004;8(4):r204-12.

26. Mehta RL, Kellum JA, Shah S V., Molitoris BA, Ronco C, Warnock DG, et al. Acute

kidney injury network: Report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11(2):1–8.

27. KDIGO. Clinical practice guideline for acute kidney injury (AKI). Kidney Int Suppl. 2012;2(1):4.

28. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. [Internet]. The Cochrane Collaboration. 2011. Available from: http://handbook.cochrane.org

29. Petra M, D. WS, Les I. A comparison of methods to detect publication bias in meta-analysis. Stat Med. 2001;20(4):641–54.

30. Lau J, Ioannidis JP, Terrin N, Schmid C, Olkin I. The case of the misleading funnel plot. Br Med J. 2006;333(7568):597–600.

31. Dalton JE, Bolen SD, Mascha EJ. Publication Bias: The elephant in the review. Anesth Analg. 2016;123(4):812–3.

32. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539–58.

33. Turner S, Derham C, Orsi NM, Bosomworth M, Bellamy MC, Howell SJ. Randomized clinical trial of the effects of methylprednisolone on renal function after major vascular surgery. Br J Surg. 2008;95(1):50-56.

34. Garg AX, Devereaux PJ, Hill A, Sood M, Aggarwal B, Dubois L, et al. Oral curcumin in elective abdominal aortic aneurysm repair: A multicentre randomized controlled trial. Can

Med Assoc J. 2018;190(43):E1273–80.

35. Wijnen MH, Vader HL, Van Den Wall Bake AW, Roumen RM. Can renal dysfunction after infra-renal aortic aneurysm repair be modified by multi-antioxidant supplementation? J Cardiovasc Surg (Torino). 2002;43(4):483-488.

36. Lau LL, Halliday MI, Smye MG, Lee B, Hannon RJ, Gardiner KR, et al. Extraperitoneal approach reduces intestinal and renal dysfunction in elective abdominal aortic aneurysm repair. Int Angiol. 2001;20(4):282-287.

37. de Almeida Mendes C, de Arruda Martins A, Teivelis MP, Kuzniec S, Varella AYM, Wolosker N. Carbon dioxide as contrast medium to guide endovascular aortic aneurysm repair. Ann Vasc Surg. 2017;39:67-73.

38. Saratzis A, Chiocchia V, Jiffry A, Hassanali N, Singh S, Imray CH, et al. Hydration and bicarbonate to prevent acute renal injury after endovascular aneurysm repair with suprarenal fixation: pilot/feasibility randomised controlled study (HYDRA pilot trial). Eur J Vasc Endovasc Surg. 2018;55(5):648–56.

39. Bonazzi M, Gentile F, Biasi GM, Migliavacca S, Esposti D, Cipolla M, et al. Impact of perioperative haemodynamic monitoring on cardiac morbidity after major vascular surgery in low risk patients. A randomised pilot trial. Eur J Vasc Endovasc Surg. 2002;23(5):445–51.

40. Mahmood A, Gosling P, Vohra RK. Randomized clinical trial comparing the effects on renal function of hydroxyethyl starch or gelatine during aortic aneurysm surgery. Br J Surg. 2007;94(4):427-433.

41. Kalimeris K, Nikolakopoulos N, Riga M, Christodoulaki K, Moulakakis KG, Dima C, et al. Mannitol and renal dysfunction after endovascular aortic aneurysm repair procedures: A randomized trial. J Cardiothorac Vasc Anesth. 2014;28(4):966–71.

42. Moore NN, Lapsley M, Norden AG, Firth JD, Gaunt ME, Varty K, et al. Does N-acetylcysteine prevent contrast-induced nephropathy during endovascular AAA repair? A randomized controlled pilot study. J Endovasc Ther. 2006;13(5):660–6.

43. Mitaka C, Kudo T, Jibiki M, Sugano N, Inoue Y, Makita K, et al. Effects of human atrial natriuretic peptide on renal function in patients undergoing abdominal aortic aneurysm repair. Crit Care Med. 2008;36(3):745–51.

44. Mouton R, Pollock J, Soar J, Mitchell DC, Rogers CA. Remote ischaemic preconditioning versus sham procedure for abdominal aortic aneurysm repair: an external feasibility randomized controlled trial. Trials. 2015;16(1):377.

45. Murphy N, Vijayan A, Frohlich S, O'Farrell F, Barry M, Sheehan S, et al. Remote ischemic preconditioning does not affect the incidence of acute kidney injury after elective abdominal aortic aneurysm repair. J Cardiothorac Vasc Anesth. 2014;28(5):1285-1292.

46. Walsh SR, Boyle JR, Tang TY, Sadat U, Cooper DG, Lapsley M, et al. Remote ischemic preconditioning for renal and cardiac protection during endovascular aneurysm repair: a randomized controlled trial. J Endovasc Ther. 2009;16(6):680–9.

47. Walsh SR, Sadat U, Boyle JR, Tang TY, Lapsley M, Norden AG, et al. Remote ischemic preconditioning for renal protection during elective open infrarenal abdominal aortic aneurysm repair: randomized controlled trial. Vasc Endovascular Surg. 2010;44(5):334–

40.

48. Ali ZA, Callaghan CJ, Lim E, Ali AA, Nouraei SAR, Akthar AM, et al. Remote ischemic preconditioning reduces myocardial and renal injury after elective abdominal aortic aneurysm repair: a randomized controlled trial. Circulation. 2007;116(11):98-105.

49. Li C, Li Y-S, Xu M, Wen S-H, Yao X, Wu Y, et al. Limb remote ischemic preconditioning for intestinal and pulmonary protection during elective open infrarenal abdominal aortic aneurysm repair: A randomized controlled trial. Anesthesiology. 2013;118(4):842–52.

50. Myburgh JA, Finfer S, Bellomo R, Billot L, Cass A, Gattas D, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med. 2012;367(20):1901–11.

51. Perner A, Haase N, Guttormsen AB, Tenhunen J, Klemenzson G, Aneman A, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med. 2012;367:124–34.

52. Weisbord SD, Gallagher M, Jneid H, Garcia S, Cass A, Thwin S-S, et al. Outcomes after angiography with sodium bicarbonate and acetylcysteine. N Engl J Med. 2018;378(7):603–14.

53. Park M, Coca SG, Nigwekar SU, Garg AX, Garwood S, Parikh CR. Prevention and treatment of acute kidney injury in patients undergoing cardiac surgery: A systematic review. Am J Nephrol. 2010;31(5):408–18.

54. Chawla LS, Eggers PW, Star RA, Kimmel PL. Acute kidney injury and chronic kidney

disease as interconnected syndromes. N Engl J Med. 2014;371(1):58–66.

55. Jüni P, Holenstein F, Sterne J, Bartlett C, Egger M. Direction and impact of language bias in meta-analyses of controlled trials: Empirical study. Int J Epidemiol. 2002;31(1):115–23.

56. Moher D, Klassen TP, Schulz KF, Berlin JA, Jadad AR, Liberati A. What contributions do languages other than English make on the results of meta-analyses? J Clin Epidemiol. 2000;53(9):964–72.

Chapter 5

5 Integrated Discussion

The objectives of this thesis are revisited integrating the results and conclusions of chapters 1 through 4. The preventive strategies for AKI following AAA repair discussed in this thesis are summarized and interpreted in sections 5.1 through 5.3 respectively, including: a summary of findings, the strengths and limitations of this work and proposed future directions.

5.1 Summary of Findings

We explored potential therapeutic targets for the prevention of AKI following AAA repair. We examined the risk of AKI following AAA repair among patients taking preoperative ACE inhibitors and/or ARBs within 24 hours of repair. We also examined the risk of AKI following AAA repair among patients who experience intraoperative hypotension (SBP <100mmHg) and were subsequently treated with fluids, inotropes/vasopressors or no treatment. In our data set, we found no significant association between ACE inhibitor and/or ARB immediate preoperative use and AKI among AAA repair patients (OR=1.3, 95% CI 0.8 – 2.2). We found no significant association between intraoperative hypotension (SBP < 100mmHg) and associated treatments and AKI among AAA repair patients in a multivariable logistic regression analysis (No treatment: OR=2.0 95% CI 0.8 – 4.8, Fluids: OR=1.0 95% CI 0.4 – 2.6, Inotropes/Vasopressors: OR=1.7 95% CI 0.8 – 3.7). In Chapter 4, we explored preventive strategies for AKI among AAA repair patients in a systematic review and meta-analysis of RCTs. Interventions that were shown to have a potential beneficial effect include mannitol, a composite of antioxidant supplements, an open extraperitoneal approach and human atrial natriuretic peptide.

Our finding that ACE inhibitor and/or ARB use within 24 hours of repair were not significantly associated with AKI among AAA repair patients is somewhat consistent with the literature available among this patient setting. Zabrocki et al. did not determine a significant association among this patient setting, however Statius et al determined a significant association between ACE/ARB use and postoperative AKI (OR 4.1 95% CI 1.4 – 12.1) among 212 EVAR patients.[1,2] Pisimisis et al. found a trend towards a possible association however it did not reach statistical significance (P=0.07).[3] There is no clear consensus whether to continue or discontinue ACE inhibitors and/or ARBs among AAA repair patients. Our analysis would add further evidence that discontinuing these medications may not be necessary to prevent AKI, however, our analysis is not definitive.

We identified intraoperative hypotension, particularly when treated with inotropes/vasopressors rather than fluids, to be associated with higher odds of AKI on bivariate analysis as stated earlier. This association was not statistically significant when we adjusted for relative covariates, however, the point estimates remained in the same direction. There is a sound pathophysiologic rationale that intraoperative hypotension would potentiate AKI development after AAA repair, and is consistent with prior literature on the subject.[4–8] Most studies have found a significant association with AKI, including Tallgren et al which determined intraoperative hypotension to be a significant risk factor following multivariable analysis.[5] Our study is unique in that we examined the effect of different methods of treatment for the hypotension (nothing, fluids or inotropes/vasopressors) and its effects on AKI. Although the evidence is very weak, our results suggest avoidance of hypotension, and if it occurs treatment with fluids rather than inotropes/vasopressors, may help reduce the risk of AKI. These speculative findings warrant further study to confirm these potential preventive effects.

In Chapter 4, we systematically summarized the existing literature on potential interventions to reduce AKI after AAA repair including mannitol, a composite of antioxidant supplements, an open extraperitoneal approach and hANP. Curcumin, methylprednisolone, carbon dioxide contrast medium, haemodynamic monitoring and N-acetylcysteine were identified to be ineffective. We meta-analyzed 6 trials studying remote ischemic preconditioning (RIPC) which showed no statistically significant difference between RIPC and standard treatment (OR 1.2, 95% CI 0.4 - 3.9). The included trials were small, at high risk of bias and inconsistent. This review identified the large gap in knowledge relevant to effective preventive strategies for this important complication following AAA repair. Several potential targets were identified, but larger, well-designed, prospective trials are needed to further guide therapeutic efforts.

5.2 Strengths and Limitations

5.2.1 Strengths

We performed a secondary data analysis of the largest RCT done to date on the topic of AKI and AAA repair. Our data set is of high quality from a prospectively collected RCT. Our data were collected across 10 centres in Canada over 4 provinces allowing for generalizability in Canada. Our variables were all diagnosed by a practitioner and were adjudicated by a third party blinded to randomization. This strength in our study can help to estimate the true event rate of AKI as diagnostic codes are known to underestimate the true event rate. Our analysis of intraoperative hypotension and associated treatments is unique as this information is not available in the existing literature. AKI was diagnosed according to the KDIGO criteria which has not been used in most studies.[9]

In Chapter 4, our systematic review was performed according to the Cochrane collaboration handbook and reported using the PRISMA guidelines. A comprehensive search of relevant literature screened over 5000 studies. The screening, selection, eligibility criteria assessment and data extraction was completed independently by two reviewers to minimize bias. We limited included studies to RCTs to focus on potentially more impactful research.

5.2.2 Limitations

In Chapter 3, out secondary data analysis was limited by residual confounding despite the data being prospectively collected. The data were limited only to Canada and a predominantly white sample. Our analysis was underpowered, and our exposures of interest were not of main interest in the initial analysis and this limited the secondary data analysis. The dose of ACE inhibitors and/or ARBs was not considered and could have an impact on the results. Although we were able to separate out patients who simply held their ACE inhibitors/ARBs from those who were not on the medication at all when assessing whether receiving the medication before surgery made a difference or not in odds of AKI in a subgroup analysis, our multivariable analysis was significantly underpowered to detect a difference.

Our measure of intraoperative hypotension was restricted to a dichotomous variable (>100 or <100 systolic BP). We did not take into account the magnitude of the hypotension, nor the amount of hypotensive time, and as such we did not have the granularity to fully explore the potential relationship between this measure and AKI. It is possible that had we used more severe criteria for hypotension (<80 systolic for example) or considered the amount of time the patient was hypotensive; we may have identified a stronger association between this and AKI. Similarly, our measure of the interventions used to treat the hypotension were crude and dichotomous

(fluids: yes or no; inotropes/vasopressors: yes or no) and further granularity here would have also been beneficial. Unfortunately, we were limited by the data that had been collected. Our data is also likely to underestimate the effects of intraoperative hypotension as anesthesiologists tend to underreport negative intraoperative blood pressures instead presenting a "smoother" variation.[10]

In Chapter 4, our systematic review and meta-analysis was limited to English studies only and the studies identified were generally small, single-centre, low quality and underpowered. The definitions of AKI across studies was highly variable and only one used the recently identified KDIGO criteria. The poor-quality and paucity of the existing RCT literature thus limited any firm conclusions we could make regarding effective measures for the prevention of AKI after AAA repair.

5.3 Conclusion and Future Directions

Among AAA repair patients, we found no evidence to suggest that there is a statistically significant association between patients who received an ACE inhibitor and/or ARB within 24 hours prior to repair and postoperative AKI compared with patients who did not. The use of ACE inhibitors or ARBs preoperatively should be evaluated on a case by case basis depending on the individual patients hypertension preoperatively. Future studies should evaluate the use of these drugs in a well powered, high quality RCT as they remain a point of interest. Future studies should consider the timing of administration of ACE/ARBs and their dosage with a defined protocol. We found no statistically significant association between postoperative AKI with any treatment for intraoperative hypotension when compared to those without hypotension. A possible trend across the bivariate and multivariable analyses suggest an association between inotrope/vasopressor treatment or no treatment with postoperative AKI compared with patients without intraoperative hypotension. Our data suggests the possibility that fluids would be a better

treatment option compared with inotropes/vasopressors, but this association should be further studied in a large, high quality, multi-centre RCT. Future studies should not only consider treatment of intraoperative hypotension but should also consider the severity and duration of the hypotensive episode. Our systematic review and meta-analysis has identified a few potential targets for further study including mannitol, a composite of antioxidant supplements, an open extraperitoneal approach and hANP. Among patients undergoing elective AAA repair, the lack of available literature for preventive strategies for AKI highlight the need for large, high quality, multi-centre RCTs to identify interventions for reducing the incidence of postoperative AKI, mortality and RRT using appropriate endpoints and definitions of variables.

5.4 References

1. Statius van Eps RG, Nemeth B, Mairuhu RTA, Wever JJ, Veger HTC, van Overhagen H, et al. Determinants of acute kidney injury and renal function decline after endovascular abdominal aortic aneurysm repair. Eur J Vasc Endovasc Surg. 2017;54(6):712–20.

2. Zabrocki L, Marquardt F, Albrecht K, Herget-Rosenthal S. Acute kidney injury after abdominal aortic aneurysm repair: current epidemiology and potential prevention. Int Urol Nephrol. 2018 Feb;50(2):331–7.

3. Pisimisis GT, Bechara CF, Barshes NR, Lin PH, Lai WS, Kougias P. Risk factors and impact of proximal fixation on acute and chronic renal dysfunction after endovascular aortic aneurysm repair using glomerular filtration rate criteria. Ann Vasc Surg. 2013;27(1):16–22.

4. Yue J-N, Luo Z, Guo D-Q, Xu X, Chen B, Jiang J-H, et al. Evaluation of acute kidney injury as defined by the risk, injury, failure, loss, and end-stage criteria in critically ill patients undergoing abdominal aortic aneurysm repair. Chin Med J (Engl). 2013;126(3):431–6.

5. Tallgren M, Niemi T, Poyhia R, Raininko E, Railo M, Salmenpera M, et al. Acute renal

injury and dysfunction following elective abdominal aortic surgery. Eur J Vasc Endovasc Surg. 2007;33(5):550–5.

6. Goren O, Matot I. Perioperative acute kidney injury. Br J Anaesth. 2015;115:3–14.

7. Brinkman R, HayGlass KT, Mutch WAC, Funk DJ. Acute kidney injury in patients undergoing open abdominal aortic aneurysm aepair: A pilot observational trial. J Cardiothorac Vasc Anesth. 2015;29(5):1212–9.

8. Hobson C, Lysak N, Huber M, Scali S, Bihorac A. Epidemiology, outcomes, and management of acute kidney injury in the vascular surgery patient. J Vasc Surg. 2018;68(3):916–28.

9. KDIGO. Clinical practice guideline for acute kidney injury (AKI). Kidney Int Suppl. 2012;2(1):4.

10. Block FE. Normal fluctuation of physiologic cardiovascular varibales during anesthesia and the phenomenon of "smoothing". J Clin Monit Comput. 1991; 7(2): 141-145.

6 Appendices

Appendix A: Inclusion and exclusion criteria from the curcumin trial

Inclusion criteria for patients at pre-operative assessment scheduled for an elective repair of an unruptured AAA (excluding thoracic and thoracoabdominal aneurysms) included: age greater than 18 years, ability to provide written consent, if the participant is diabetic they were willing to monitor and record glucose levels at home, and an open repair or an endovascular repair where the patient had at least one of the following risk factors for post-operative complications: i) diabetes mellitus treated with insulin or oral hypoglycemic agents, ii) age greater than 70 years, or iii) an elevated preoperative serum creatinine (> 177 μmol/L (2.0 mg/dL) in men or > 146 μmol/L (1.6 mg/dL) in women). Patients were excluded according to the following criteria: patients requiring an elective AAA repair expected to occur in ≤ 3 days, a prior kidney transplant, patients who were pregnant or breastfeeding, current active gastrointestinal reflux disease, gastrointestinal ulcer, or hepatobiliary disease, evidence of AKI in the 30 days prior to pre-operative assessment, participating in another study that could conflict with the intervention or outcomes of the trial, received 1 or more dialysis treatments (hemodialysis or peritoneal dialysis) in the week prior to assessment, previous participation in this trial, a history of a major bleeding event in the 6 months prior to assessment, a bleeding disorder (a diagnosis of hemophilia, von Willibrand disease, platelets <70), an allergy to turmeric, ginger, curry, cumin, cardamom, yellow or red food coloring, gelatin or cellulose and a history of hypoglycemia in the 6 months prior to assessment (<3.5 mmol/L or < 135.0 mg/dL).

Appendix B In depth description of mediation analysis methods

To determine whether to use the traditional mediation approach of Baron and Kenny (1986), structural equation modeling or the counterfactual approach by Robins and Greenland (1992) we considered two factors.[1,2] The first factor is a possible interaction between the exposure and mediator which would require the use of the counterfactual approach. However, there was no significance for the interaction variable modelled using an interaction term in the multivariable logistic regression adjusting for various confounders ($p>0.05$). The second factor being that the mediator and the outcome are binary which requires a method that uses a unified approach which cannot be satisfied with structural equation modelling. Therefore, mediation was assessed using the counterfactual framework by Robins and Greenland (1992) with the definitions developed by VanderWeele and Vansteelandt (2009-2010).[3,4] Valeri and VanderWeele (2013) provided the definitions for binary mediators.[5] Confounding is controlled for using covariates with the regression approach of VanderWeele (2014).[6] The CAUSALMED procedure in SAS fits generalized linear models that have binary distributions for the outcome and for the mediator. Covariate effects are incorporated in both the outcome and mediator models. The model estimates are then used to compute various mediator effects including total effect (TE), controlled direct effect (CDE), natural direct effect (NDE) and natural indirect effect (NIE) on the odds ratio scale.[5,6]

1. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic and statistical considerations. J. Pers. Soc. Psychol. 1986; 51(6): 1173-1182.

2. Robins JM, Greenland S. Identifiability and exchangeability for direct and indirect effects. Epidemiology. 1992; 3(2): 143-155.

3. VanderWeele TJ, Vansteelandt S. Conceptual issues concerning mediation, interventions and composition. Stat Interface.

4. VanderWeele TJ, Vansteelandt S. Odds ratios for mediation analysis for a dichotomous outcome. Am. J. Epidemiol. 2010; 172(12): 1339-1348.

5. Valeri L, VanderWeele TJ. Mediation analysis allowing for exposure-mediator interactions and causal interpretation: theoretical assumptions and implementation with SAS and SPSS macros. Psychol. Methods. 2013; 18(2): 137-150.

6. VanderWeele TJ. A unification of mediation and interaction: a four-way decomposition. Epidemiology. 2014; 25(5): 749-761.

Appendix C Comparison of baseline, preoperative and operative characteristics between patients with and without postoperative AKI

	AKI N=79	No AKI N=522	*P* value
Age, (years) mean (SD)	73.5, (8.5)	75.8, (7.8)	*P*=0.02
Sex, male, No. (%)	59 (74.7%)	437 (83.7%)	*P*=0.049
Centre			
London	27 (34.2%)	180 (34.5%)	
Edmonton	21 (26.6%)	155 (29.7%)	
Ottawa	13 (16.5%)	38 (7.3%)	
Hamilton	4 (5.1%)	47 (9.0%)	
Winnipeg	3 (3.8%)	31 (5.9%)	
Sudbury	5 (6.3%)	17 (3.3%)	*P*=0.22
Toronto – St. Michael's Hospital	3 (3.8%)	15 (2.9%)	
Toronto – Sunnybrook	2 (2.5%)	14 (2.7%)	
Calgary	1 (1.3%)	14 (2.7%)	
Montreal	0 (0.0%)	11 (2.1%)	
Diabetes mellitus, No. (%)	19 (24.1%)	125 (24.0%)	*P*=0.98
Hypertension, No. (%)*	70 (88.6%)	387 (74.4%)	*P*<0.01
Pre-existing chronic kidney disease (GFR < 60 mL/min/1.73m2)	36 (45.6%)	155 (29.7%)	*P*<0.01
Repair type performed, No. (%)			
Open	61 (77.2%)	221 (42.3%)	*P*<0.0001
EVAR	18 (22.8%)	301 (57.7%)	
Aneurysm size, (mm) mean (SD)	57.9, (14.8)	57.5, (11.0)	*P*=0.76
Complications**, No. (%)	21 (26.6%)	33 (6.3%)	*P*<0.0001
Death, No. (%)	5 (6.4%)	4 (0.8%)	*P*<0.01

*2 patients missing hypertension information, **Complications include new acute dialysis, myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft, sepsis, pneumonia, non-fatal cardiac arrest, stroke, deep vein thrombosis, pulmonary embolism, lower limb amputation, ischemic bowel, congestive heart failure, death within 30 days of surgery), *** death within 30 days of surgery.
AKI, acute kidney injury, SD, standard deviation, EVAR, endovascular, No., number of patients, frequency.

Appendix D Further adjustment of multivariable models to account for centre

Exposure		Adjusted Odds Ratio (95%	Adjusted Odds Ratio – further adjusted for centre with a random intercept for each centre (95% CI)
ACE/ARB*		1.3 (0.8 – 2.2)	1.3 (0.7 – 2.3)
SBP <100mmHg**			
	No treatment	2.0 (0.8 – 4.8)	1.7 (0.7-4.2)
	Fluids	1.0 (0.4 – 2.6)	1.0 (0.4-2.6)
	Inotropes/Vasopressors	1.7 (0.8 – 3.7)	1.8 (0.8-3.9)

* Adjusting for Age, Pre-existing CKD, Repair Type Performed (Open vs. EVAR), DM, HTN, intraoperative SBP < 100 mmHg, and Aneurysm Diameter

** Adjusting for Age, Pre-existing CKD, Repair Type Performed (Open vs. EVAR), DM, HTN, and Aneurysm Diameter

ACE, angiotensin-converting enzyme inhibitor, ARB, angiotensin II receptor blocker, SBP, systolic blood pressure, AKI, acute kidney injury, CI, confidence interval, CKD, chronic kidney disease, EVAR, endovascular abdominal aortic aneurysm repair, DM, diabetes mellitus, HTN, hypertension.

Appendix E. Search Strategies for Systematic Review in various databases

Concept	AKI	Abdominal Aortic Aneurysm
Keywords	Acute kidney injur* OR acute kidney failure OR acute kidney insufficienc* OR acute renal injur* OR Acute renal failure OR acute renal insufficienc* OR renal protect* OR renoprotect* OR kidney protect* OR nephroprotect* OR reno-protect* OR nephro-protect*	abdominal aneurysm* OR abdominal aortic OR endovascular AAA OR open AAA OR EVAR OR endovascular aneurysm*
Medline	kidney diseases/ or renal insufficiency/ or acute kidney injury/	Aortic Aneurysm, Abdominal/ OR Aortic Aneurysm/
EMBASE	acute kidney failure/ or kidney failure/ or kidney disease/ or renal protection/	abdominal aortic aneurysm/ or aortic aneurysm/ or descending aortic surgery/ or endovascular aneurysm repair/ or aneurysm surgery/
CINAHL	(MH "Renal Insufficiency") OR (MH "Kidney Failure, Acute") OR (MH "Kidney Diseases")	(MH "Aortic Aneurysm, Abdominal") OR (MH "Aortic Aneurysm")
Web of Science	TS=("Acute kidney injur*" OR "acute kidney failure" OR "acute kidney insufficienc*" OR "acute renal injur*" OR "acute renal failure" OR "acute renal insufficienc*" OR “renal protect*” OR “renoprotect*” OR “kidney protect*” OR “nephroprotect*” OR “reno-protect*” OR “nephro-protect*”)	TS=(“abdominal aneurysm*” OR “abdominal aortic” OR “endovascular AAA” OR “open AAA” OR “EVAR” OR “endovascular aneurysm*”)
Scopus	(TITLE-ABS-KEY("Acute kidney injur*" OR "acute kidney failure" OR "acute kidney insufficienc*" OR "acute renal injur*" OR "acute renal failure" OR "acute renal insufficienc*" OR “renal protect*” OR “renoprotect*” OR “kidney protect*” OR “nephroprotect*” OR “reno-protect*” OR “nephro-protect*”))	(TITLE-ABS-KEY("abdominal aneurysm" OR "aortic aneurysm" OR "endovascular AAA" OR "open AAA" OR “EVAR” OR “endovascular aneurysm*”))
Cochrane Library	[mh ^"kidney diseases"] or [mh ^"renal insufficiency"] or [mh ^"acute kidney injury"]	[mh ^"Aortic Aneurysm, Abdominal"] OR [mh ^"Aortic Aneurysm"]

Curriculum Vitae

Name:	Michaela Fernandes
Post-secondary Education and Degrees:	The University of Western Ontario London, Ontario, Canada 2013-2017 B.Sc.
	The University of Western Ontario London, Ontario, Canada 2017-2019 M.Sc.
Honours and Awards:	Western Graduate Research Scholarship 2017-2019

Publications:

Articles, Peer Reviewed, Published

Kiaii, B., Fox, S., Chase, L., **Fernandes, M**., Stitt, LW., Guo, R., Quantz, MW., Chu, M., Koka, P., McClure, RS., McKenzie, FN., Klein, GJ., Novick, RJ., Skanes, AC. (2015). Postoperative Atrial Fibrillation is not Pulmonary Vein Ablation Dependent: Results from a randomized trial. *Heart Rhythm*, 12(4), 699-705. Published January 13th, 2015.

Articles, Peer Reviewed, In Press

Thibeault, PE., LeSarge, JC., Arends, A., **Fernandes, M.,** Chidiac, P., Stathopulos, PB., Luyt, LG., Ramachandran, R. (2019). Molecular Basis for G-protein-Coupled Receptor (GPCR) Activation and Biased Signalling at the Platelet Thrombin Receptor Proteinase Activated Receptor-4 (PAR4). *J Biol Chem*, Accepted.

Articles, In Preparation

Fernandes, M., Majoni, M., Garg, AX., Dubois, L. (2019). Systematic review and meta-analysis of preventative strategies for acute kidney injury in patients undergoing elective abdominal aortic aneurysm repair. In preparation.

Conference Posters and Presentations:

Fernandes, M (presenter), Majoni, M, Garg, AX, Dubois, L. Systematic review and meta-analysis of preventative strategies for acute kidney injury in patients undergoing elective abdominal aortic aneurysm repair. Oral presentation at: Canadian Society of Vascular Surgery Annual Meeting, Kelowna BC, Canada; 2019 September 13-14.

Fernandes, M (presenter), Majoni, M, Garg, AX, Dubois, L. Systematic review and meta-analysis of preventative strategies for acute kidney injury in patients undergoing elective abdominal aortic aneurysm repair. Poster presented at: Department of Surgery Research Day, London, ON, Canada. 2019 June 24.

Fernandes, M (presenter), Majoni, M, Garg, AX, Dubois, L. Systematic review and meta-analysis of preventative strategies for acute kidney injury in patients undergoing elective abdominal aortic aneurysm repair. Poster presented at: Canadian Society of Epidemiology and Biostatistics Biennial National Conference, Ottawa, ON, Canada 2019 May 13-15.

Fernandes, M (presenter), Majoni, M, Garg, AX, Klar, N, Dubois, L. Identifying Preventative Strategies for Acute Kidney Injury in Patients Undergoing Abdominal Aortic Aneurysm Repair. Poster presented at: Canadian Society of Epidemiology and Biostatistics Biennial National Conference, Ottawa, ON, Canada 2019 May 13-15.

Fernandes, M (presenter), Majoni, M, Garg, AX, Dubois, L. Systematic review and meta-analysis of preventative strategies for acute kidney injury in patients undergoing elective abdominal aortic aneurysm repair. Poster presented at: London Health Research Day, London ON, Canada, 2019 April 30.

Thibeault, P (presenter), Lesarge, JC, D'Arcy, A, **Fernandes**, **M**, Luyt, L, Ramachandran, R. Insights into Proteinase Activated Receptor 4 (PAR4) signaling, trafficking and biased agonism. Poster presented at: 18th World Congress of Basic & Clinical Pharmacology, Kyoto, Japan, 2018 July.

Fernandes, M (presenter). Structure Activity Relationship (SAR) Study of the Protease Activated Receptor 4. Oral presentation at: 45th Southwestern Ontario Undergraduate Student Chemistry Conference, 2017 March.