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Preoperative Angiotensin Converting Enzyme Inhibitor or Angiotensin Receptor Blocker Use and Acute Dialysis: A Population Based Cohort Study

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A thesis submitted in partial fulfillment of the requirements for the degree in Master of Science

PREOPERATIVE ANGIOTENSIN CONVERTING ENZYME INHIBITOR OR ANGIOTENSIN RECEPTOR BLOCKER USE AND ACUTE DIALYSIS: A POPULATION BASED COHORT STUDY

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ABSTRACT

Angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) use prior to major surgery is controversial. We performed a population based retrospective cohort study of 237,208 elderly patients (of whom 101,494 (42.8%) were ACEi or ARB users) who underwent major elective surgery from 1995 to 2010 in Ontario, Canada. The primary outcome was acute kidney injury treated with dialysis (AKI-D) within 14 days following surgery (810 (0.34%) patients). The secondary outcome was all-cause mortality within 90 days following surgery (11,089 (4.67%) patients). After adjusting for potential confounders, preoperative ACEi or ARB use was associated with a lower relative risk of AKI-D (adjusted relative risk (RR): 0.83; 95% confidence interval (CI): 0.71 to 0.98) and a lower relative risk of all-cause mortality (adjusted RR: 0.91; 95% CI: 0.87 to 0.95). Results were consistent in propensity score matched analyses. We observed a significant effect modification by chronic kidney disease on AKI-D (p-value < 0.0001). Randomized controlled trials are needed to clarify this issue.

Keywords: Angiotensin converting enzyme inhibitor, angiotensin receptor blocker, acute kidney injury treated with dialysis, retrospective cohort study, elective surgery, all-cause mortality, relative risk, propensity score matched analyses, chronic kidney disease, randomized controlled trials

DEDICATION

I dedicate this thesis to my parents for their love and encouragement throughout my life and my sister, Dhara.

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CHAPTER 1 – INTRODUCTION

1.1 Acute Kidney Injury

Acute kidney injury (AKI) is sudden decline in renal function and severe AKI can require treatment with dialysis.[1-5] Hospital admission with AKI is associated with a longer hospital length of stay and a higher risk of mortality.[6;7] In the United States, AKI accounts for yearly health care expenditures in excess of ten billion dollars.[6]

1.2 Major surgeries can be complicated by acute kidney injury treated with dialysis

Approximately 1.25 million patients undergo cardiac surgery around the world every year.[8] About 1% of patients (12,500 patients) develop AKI treated with dialysis (AKI-D).[2;3;8;9] Approximately 225 million patients undergo non-cardiac surgery worldwide every year.[10] The risk of AKI-D in non-cardiac surgeries is particularly high with vascular, thoracic, abdominal, and retro-peritoneal surgeries.[4;11-14] About 0.4% of patients (900,000 patients) undergoing non-cardiac surgery develop AKI-D.[15-17]

Postoperative AKI occurs as a result of decreased renal perfusion which causes a hypoxic insult, followed by activation of inflammatory mediators, proinflammatory transcription factors, and adhesion molecules which subsequently lead to AKI (Figure 1 and Figure 2).[18;19] There are several clinical factors that may influence a patient's risk for developing postoperative AKI. Chronic kidney disease is considered to be the most important risk factor, while other comorbidities such as congestive heart failure, coronary artery disease, hypertension, and diabetes may also increase the risk of postoperative AKI.[11;13;20] Perioperative clinical factors such as hypotension, blood loss, volume depletion, and

administration of vasoconstrictor agents may all increase the risk of postoperative AKI.[19;21]

Some preoperative medications may also influence the risk of postoperative AKI.[17] This is particular true for angiotensin converting enzyme inhibitor (ACEi) and angiotensin receptor blocker (ARB), which is the focus of this dissertation given the possibility of modification prior to planned elective surgeries.[12;21-28]

1.3 Angiotensin converting enzyme inhibitor and angiotensin receptor blocker

ACEi and ARB are therapeutic drug classes that inhibit the renin-angiotensin system.[25;29;30] ACEi inhibits angiotensin converting enzyme primarily formed in the pulmonary vasculature and prevents formation of angiotensin II from angiotensin I.[25] ARB competitively replace angiotensin II from the angiotensin I receptor and prevents angiotensin II mediated effects.[30] ACEi was first introduced in 1981 for the treatment of hypertension.[25] Since then, ACEi has proven to be beneficial in a variety of clinical conditions.[25] Chronic ACEi and ARB use in the outpatient settings reduces the risk of mortality, stroke, and myocardial infarction (fatal and non-fatal).[25;30] Patients with comorbid conditions such as congestive heart failure, atherosclerotic cardiovascular disease, diabetes mellitus, and chronic kidney disease benefit from using ACEi and ARB medications.[25;29;31] Several international randomized controlled trials such as HOPE, EUROPA, PEACE, OPTIMAAL, VALIANT, and SAVE trials have also demonstrated benefits of ACEi and ARB use in reducing cardiovascular morbidity and mortality.[32-38] Due to these benefits, ACEi and ARB are highly prescribed medications: in the United States there are more than 155 million prescriptions filled each year for ACEi and more than 80 million prescriptions for ARB.[39]

1.4 Impact of preoperative ACEi or ARB use on renal function

ACEi or ARB use lowers blood pressure.[25;30] Preoperative use of these medications may exacerbate hypotension from anesthesia and may lead to renal hypoperfusion (Figure 1).[26;29;40-43] Perioperative clinical factors such as poor cardiac output, blood loss, dehydration, and administration of vasoconstrictors can all contribute to lower renal perfusion.[19;21;44] The autoregulation to renal hypoperfusion is to increase angiotensin II production, which constricts the glomerular efferent arteriole and maintains the glomerular filtration rate (GFR).[44] However, ACEi or ARB use interferes with the angiotensin II mediated autoregulation to renal hypoperfusion.[19;44] This can lead to sudden decline in GFR, hypoxic insult, followed by activation of the inflammatory response, and subsequent AKI (Figure 1).[18;19;44]

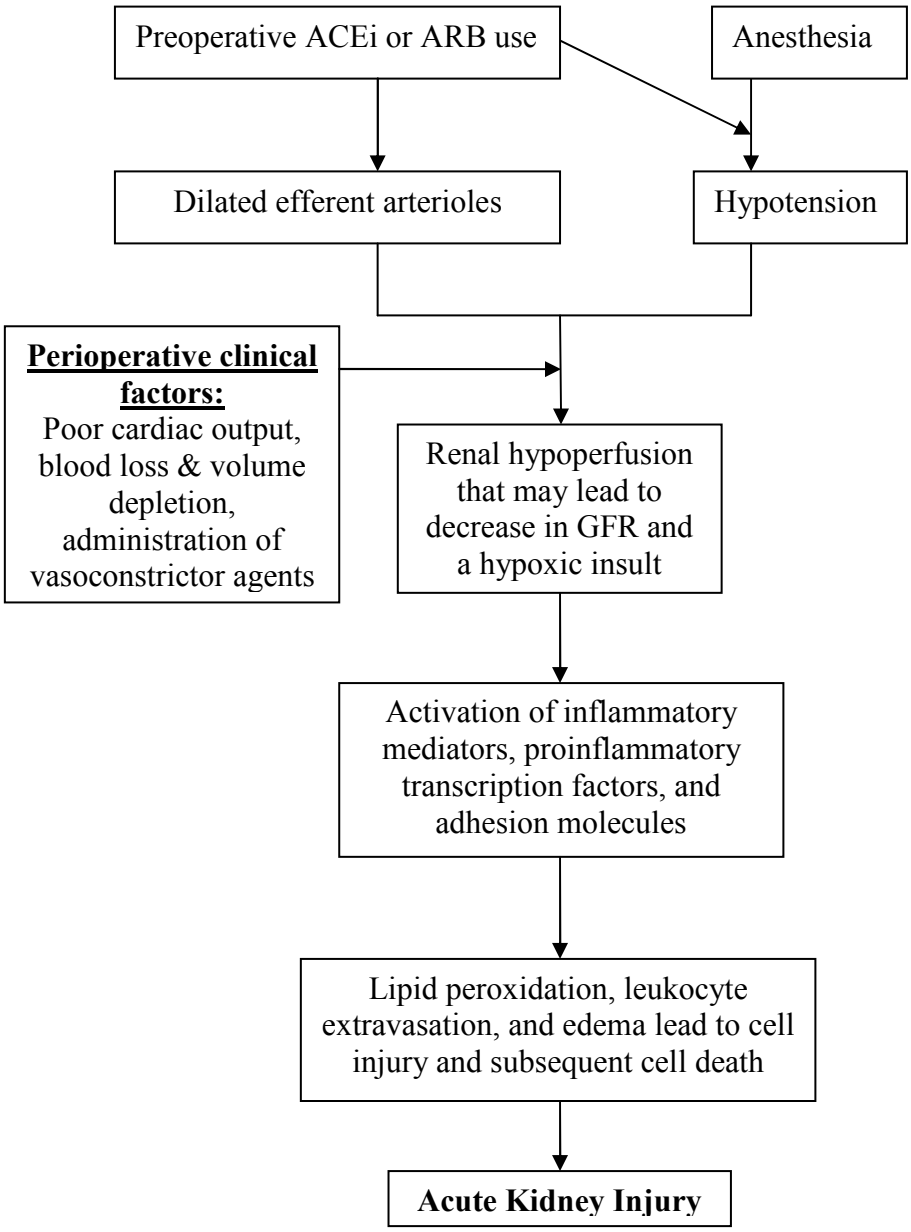
Contrary to the proposed damaging effects, ACEi or ARB use may have beneficial effects which reduce the risk of postoperative AKI (Figure 2).[23;25;29;30;45-50] ACEi and ARB medications possess vasculoprotective properties mainly through inhibition of a potent vasoconstrictor, angiotensin II.[23;25;29;30;45-50] Angiotensin II can increase the risk of postoperative AKI by accelerating oxidative stress, endothelial dysfunction, the inflammatory response, and acute ischemia, which may be mitigated by ACEi or ARB use.[23;25;29;30;46-48] ACEi or ARB use through the inhibition of angiotensin II mediated vasoconstriction can also reduce the risk of postoperative AKI by decreasing renal vascular resistance and promoting renal blood flow.[23;25;29;30;45-50]

1.5 Clinical practice guidelines: Preoperative ACEi or ARB use

There is lack of clear recommendations on whether ACEi or ARB should be withheld prior to major surgery with a marked difference in practice patterns

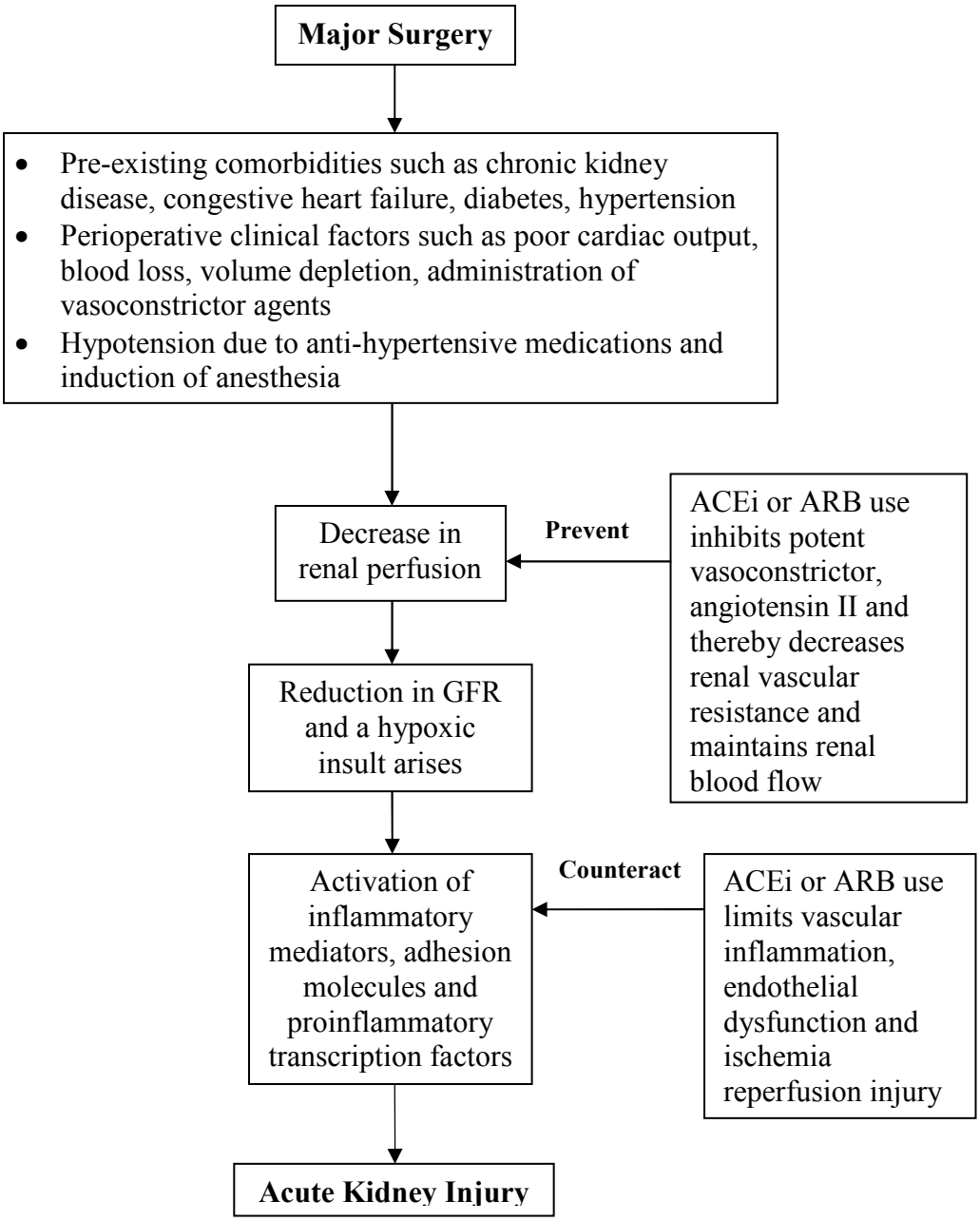
worldwide.[21;22;40;41;51-53] The American College of Cardiology (ACC) / American Heart Association (AHA) 2007 guidelines reported that several authors suggested to withhold ACEi or ARB medication the morning of surgery and to restart these medications in the postoperative period only when a patient is euvolemic.[52] This management strategy may reduce the risk of postoperative AKI but there is lack of high quality evidence to support this suggestion.[52]

Figure 1: Preoperative ACEi or ARB use may lead to AKI[18;19;26;29;40-44;54-58]



ACEi: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker;
AKI: Acute kidney injury; GFR: Glomerular filtration rate;
This figure is partly adapted from Rosner *et al*.[19]

Figure 2: Preoperative ACEi or ARB use may prevent AKI[18;19;23;25;28;46-50;54-58]



ACEi: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; AKI: Acute kidney injury; GFR: Glomerular filtration rate
This figure is partly adapted from Rosner *et al*.[19]

CHAPTER 2 – LITERATURE REVIEW

2.1 Potential risk factors for postoperative AKI

We performed a literature review to identify potential risk factors for postoperative AKI (requiring or not requiring dialysis).[4;9;11;13;17;20] We summarized the potential risk factors and their association with postoperative AKI in Table 1. Thakar *et al.*[9], in a predictive model for AKI after cardiac surgery, suggested that congestive heart failure, diabetes mellitus, chronic obstructive pulmonary disease, peripheral vascular disease, and cerebrovascular disease were potential risk factors for postoperative AKI-D. Kheterpal *et al.*[13], in a risk index for AKI after general surgery, indicated that older age (≥ 56 years), male sex, diabetes mellitus, chronic kidney disease, congestive heart failure, hypertension, and intraperitoneal surgery were all potential risk factors for postoperative AKI.

2.2 Present studies: Preoperative ACEi or ARB use and AKI

As of May 2012, 12 observational studies (11 published studies and one abstract) have examined the association between preoperative ACEi or ARB use and postoperative AKI with non-users as the comparison group.[12;21-24;26-28;49;50;59;60] Four studies described a higher risk of AKI with preoperative ACEi or ARB use [12;21;22;60], while six studies described no significant association.[26-28;49;50;59] Conversely, two studies suggested a lower risk of AKI with preoperative ACEi or ARB use.[23;24] We summarized all 12 studies in Table 2, 3, and 4.[12;21-24;26-28;49;50;59;60] In Table 5 we also summarized key baseline characteristics that differed in ACEi or ARB users and non-users in studies of postoperative AKI.[21-24;26;28;49] Characteristics such as congestive heart failure, diabetes

mellitus, hypertension, coronary artery disease, chronic kidney disease, and peripheral vascular disease were more in ACEi or ARB users compared to non-users.[21-24;26;28;49]

Table 1: Independent risk factors for postoperative AKI

Risk factors	Author	Association with postoperative AKI (requiring or not requiring dialysis)
Older age	Kheterpal *et al.*[4]	Age ≥ 59 years: Adjusted hazard ratio = 4.2 (95% CI: 2.9 to 6.0) [Reference group: age < 59 years]
	Kheterpal *et al.*[13]	Age ≥ 56 years: Adjusted hazard ratio = 1.7 (95% CI: 1.4 to 2.2) [Reference group: age < 56 years]
	Abelha *et al.*[11]	Age ≥ 65 years: OR = 1.9 (95% CI: 1.2 to 3.0) [Reference group: age < 65 years]
Male gender	Kheterpal *et al.*[13]	Adjusted hazard ratio = 1.4 (95% CI: 1.2 to 1.7)
Chronic kidney disease	Kheterpal *et al.*[13]	Chronic kidney disease (Moderate)[+]: Adjusted hazard ratio = 3.2 (95% CI: 2.8 to 3.7) Chronic kidney disease (Mild)*: Adjusted hazard ratio = 3.1 (95% CI: 2.5 to 3.9) Reference group: Patients without chronic kidney disease
	Wijeysundera *et al.*[20]	sCr > 133 μmol/L: Adjusted OR = 15.2 (95% CI: 9.6 to 24.7) 100 μmol/L < sCr ≤ 133 μmol/L: Adjusted OR = 3.1 (95% CI: 1.9 to 5.2) sCr ≤ 100 μmol/L and CrCl ≤ 60 ml/min: Adjusted OR = 2.8 (95% CI: 1.4 to 5.3) Reference group: sCr ≤ 100 μmol/L and CrCl > 60 ml/min
Hypertension	Kheterpal *et al.*[13]	Adjusted hazard ratio = 1.5 (95% CI: 1.2 to 1.9)
Diabetes – Insulin therapy	Kheterpal *et al.*[13]	Adjusted hazard ratio = 1.7 (95% CI: 1.3 to 2.3)
Diabetes – Oral therapy	Kheterpal *et al.*[13]	Adjusted hazard ratio*" = 1.3 (95% CI: 1.0 to 1.7)
Diabetes – requiring medication	Wijeysundera *et al.*[20]	Adjusted OR = 2.5 (95% CI: 1.7 to 3.6)

Congestive heart failure	Kheterpal *et al.*[13]	Adjusted hazard ratio = 2.0 (95% CI: 1.4 to 3.0)
	Abelha *et al.*[11]	OR = 3.9 (95% CI: 2.5 to 6.1)
Coronary artery disease including angina	Abelha *et al.*[11]	OR = 2.1 (95% CI: 1.3 to 3.3)
Peripheral vascular disease	Kheterpal *et al.*[4]	Adjusted hazard ratio = 4.2 (95% CI: 2.5 to 7.1)
COPD requiring treatment with bronchodilator therapy	Kheterpal *et al.*[4]	Adjusted hazard ratio = 3.0 (95% CI: 1.9 to 5.0)
Liver disease	Kheterpal *et al.*[4]	Adjusted hazard ratio = 2.4 (95% CI: 1.4 to 4.3)
Type of surgery	Kheterpal *et al.*[4]	High-risk surgery^{++}: Adjusted hazard ratio = 2.9 (95% CI: 2.0 to 4.3)
	Kheterpal *et al.*[13]	High-risk surgery*$^{+}$: Adjusted hazard ratio = 3.3 (95% CI: 2.4 to 4.7)
	Abelha *et al.*[11]	High-risk surgery$^{\#}$: OR = 3.5 (95% CI: 2.1 to 5.6)

CI: Confidence interval; OR: Odds ratio; AKI: Acute kidney injury; sCr: Serum creatinine; CrCl: Creatinine clearance; COPD: Chronic obstructive pulmonary disease; AKI-D: AKI treated with dialysis

Kheterpal *et al.*[13] studied general surgery procedures in adult patients. Postoperative AKI was defined as an increase in serum creatinine of $\geq$ 2 mg/dl or requirement of dialysis within 30 days after surgery.[13] Preoperative mild* chronic kidney disease was defined as a serum creatinine of 1.2 to 1.9 mg/dl in the 90 days prior to surgery.[13] Preoperative moderate^{+} chronic kidney disease was defined as a serum creatinine $\geq$ 2.0 mg/dl in the 90 days prior to surgery.[13] High-risk surgery*$^{+}$ included intraperitoneal surgery except hernia repairs, while the reference group included general surgery involving hernia repairs.[13] The adjusted hazard ratio*" for diabetes – oral therapy was statistically significant.[13]

Abelha *et al.*[11] studied major noncardiac surgery in adult patients. AKI was defined according to AKIN criteria.[5;11] High-risk surgeries$^{\#}$ included intrathoracic, intraperitoneal, and suprainguinal vascular procedures, while the reference group included the remaining types of major noncardiac surgery.[11]

Wijeysundera *et al.*[20] studied cardiac surgery procedures in adult patients to identify independent risk factors for postoperative AKI-D.

Kheterpal *et al.*[4] studied major noncardiac surgery procedures in adult patients with preoperative CrCl $\geq$ 80 ml/min. Postoperative AKI was defined as a CrCl $\leq$ 50 ml/min within seven days after surgery.[4] High-risk surgeries^{++} included intraperitoneal, intrathoracic, suprainguinal vascular, or surgeries involving heavy blood loss or fluid resuscitation, while reference group included remaining types of major noncardiac surgery.[4]

Table 2: Studies: Preoperative ACEi or ARB use associated with more AKI

Author	Study Design, Setting and Patient Groups	Key Results	Conclusions	Study Limitations
Cittanova *et al.*[12]	Prospective cohort study 249 patients who underwent aortic surgery over a 2 year period 23% (57 out of 249) patients were on ACEi 24.5% (61 out of 249) patients developed AKI	ACEi use was significantly associated with AKI[a]: Adjusted OR = 2.01; 95% CI: 1.05 to 3.83, p = 0.034	Preoperative ACEi use may increase the risk of AKI after aortic surgery	Single centre study Only studied aortic surgery Risk of overfitting in statistical model
Arora *et al.*[22]	Retrospective cohort study 1,358 patients who underwent cardiac surgery between 2001 and 2005 52% (706 out of 1,358) patients were on ACEi or ARB 14% (189 out of 1,358) patients developed AKI	ACEi or ARB users vs. non-users (referent): AKI[b]: Adjusted OR = 1.41; 95% CI: 1.07 to 1.85	Preoperative ACEi or ARB use may increase the risk of AKI after cardiac surgery	Two study centres Only studied cardiac surgery
Miceli *et al.*[21]	Retrospective cohort study 9,274 patients who underwent cardiac surgery between 1996 and 2008 51% (4,730 out of 9,274) patients were on ACEi or ARB Propensity score matched analysis 3,052 ACEi or ARB users were	ACEi or ARB users vs. non-users (referent): AKI[c] (7.1% vs. 5.4%; OR = 1.36; 95% CI: 1.10 to 1.67; p = 0.006) Death[d] (1.3% vs. 0.7%;	Preoperative ACEi or ARB use may increase the risk of AKI and mortality after cardiac surgery	Single centre study Only studied cardiac surgery

	matched to 3,052 non-users	OR = 2.00; 95% CI: 1.17 to 3.42; p = 0.013)		
Railton *et al*.[60]	Retrospective cohort study 883 patients who underwent open abdominal aortic aneurysm (AAA) repair between 1998 and 2005 41% (366 out of 883) patients were on ACEi or ARB Propensity score matched analysis 261 ACEi or ARB users were matched to 261 non-users	ACEi or ARB users vs. non-users (referent): AKI-D[e]: 4.6% vs. 0.8%, p = 0.013 Death[f]: 6.1% vs. 1.5%; OR = 5.00; 95% CI: 1.40 to 27.00; p = 0.008	Preoperative ACEi or ARB use may increase the risk of AKI-D and mortality after open abdominal aortic aneurysm repair	Two study centres Small sample size Only studied open abdominal aortic aneurysm repair

OR: Odds ratio; CI: Confidence interval; AKI: Acute kidney injury; ACEi: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; ESRD: End stage renal disease; AKI-D: AKI treated with dialysis

AKI[a] was defined as a >20% decrease in creatinine clearance between preoperative and postoperative period.
AKI[b] was defined as an increase in serum creatinine > 0.3 mg/dl or > 50% increase from preoperative baseline value according to the RIFLE (risk, injury, failure, loss, ESRD) classification.[1]
AKI[c] was defined as a postoperative serum creatinine level > 200 μmol/L and ≥ 1.5 times increase from preoperative baseline serum creatinine value. Death[d] occurred within 30 days after surgery.
AKI[e] was defined as a requirement of dialysis (AKI-D). Death[f] occurred within 30 days after surgery. Railton *et al*.[60] did not find a significant association between preoperative ACEi or ARB use and AKI (not requiring dialysis) (undefined).

Table 3: Studies: Preoperative ACEi or ARB use not associated with AKI

Author	Study Design, Setting and Patient Groups	Key Results	Conclusions	Study Limitations
Ouzounian *et al*.[49]	Retrospective cohort study 5,946 patients who underwent cardiac surgery between 1998 and 2007 54.9% (3,262 out of 5,946) patients were on ACEi *1,647 patients were selected to study the association with AKI	ACEi users vs. non-users (referent): AKI[j]: Adjusted OR = 0.70; 95% CI: 0.50 to 1.10; p = 0.09 Death[k]: Adjusted OR = 1.10; 95% CI: 0.80 to 1.40; p = 0.76	Preoperative ACEi use may not be associated with AKI and mortality after cardiac surgery	Single centre study Only studied cardiac surgery Risk of overfitting in statistical model for AKI
Rady *et al*.[50]	Retrospective cohort study 11,330 patients who underwent cardiac surgery between 1993 and 1996 26.7% (3,025 out of 11,330) patients were on ACEi	ACEi users vs. non-users (referent): AKI[l]: Adjusted OR = 0.90; 95% CI: 0.70 to 1.20 Death[m]: Adjusted OR = 0.90; 95% CI: 0.70 to 1.20	ACEi use prior to surgery may not be associated with AKI and mortality after cardiac surgery	Single centre study Only studied cardiac surgery
Yoo *et al.*[28]	Retrospective cohort study 472 patients who underwent cardiac surgery between 2006 and 2009 62.7% (296 out of 472) patients were on ACEi or ARB	ACEi or ARB users vs. non-users (referent): AKI[n]: Adjusted OR = 0.34; 95% CI: 0.11 to 1.10; p = 0.090	Preoperative ACEi or ARB use may not be associated with AKI after cardiac surgery	Single centre study Only studied cardiac surgery Risk of overfitting in statistical model

	20.6% (97 out of 472) patients developed AKI and 1.5% (7 out of 472) patients required AKI-D			
Barodka *et al.*[59] (Abstract)	Retrospective cohort study 6,679 patients who underwent cardiac surgery between 1994 and 2007 32.4% (2,164 out of 6,679) patients were on ACEi 36.6% (2,447 out of 6,679) patients developed AKI	ACEi users vs. non-users (referent): AKI[o]: Adjusted OR = 0.97; 95% CI: 0.88 to 1.07; p = 0.52	Preoperative ACEi use may not be associated with AKI after cardiac surgery	Single centre study Only included cardiac surgery
Kheterpal *et al.*[26]	Prospective cohort study 45,291 patients who underwent non-cardiac surgery between 2003 and 2006 20.2% (9,143 out of 45,291) patients were on ACEi or ARB Propensity score matched analysis Of the matched cohort, 3,256 patients were selected to study the association with AKI	ACEi or ARB users vs. non-users (referent): AKI[i]: 1.95% (25/1284) vs. 1.57% (31/1972), p = 0.51	Preoperative ACEi or ARB use may not be associated with AKI after non-cardiac surgery	Single centre study
Kincaid *et al.*[27]	Retrospective cohort study 1,209 patients who underwent cardiac surgery between 2000 and	Preoperative ACEi use along with intraoperative aprotinin use was significantly associated with	Preoperative ACEi use alone was not significantly associated with	Single centre study Only included

	2002 45.1% (545 out of 1,209) patients were on ACEi 3.5% patients developed AKI	AKI[p]: Adjusted OR = 2.9; 95% CI: 1.4 to 5.8; $p < 0.0001$ Neither ACEi nor aprotinin alone was significantly associated with AKI[p]	AKI after cardiac surgery	cardiac surgery Risk of overfitting in statistical model

OR: Odds ratio; CI: Confidence interval; AKI: Acute kidney injury; ACEi: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; ESRD: End stage renal disease

AKI[j] was defined as serum creatinine exceeding 176 μmol/L and > 50% increase from preoperative baseline value. *Only a subgroup of patients (1,647 patients) was considered to examine the association between preoperative ACEi use and AKI because there was no information available on AKI in the database prior to 2004. Death[k] is in-hospital mortality.

AKI[l] was defined with one of the following criteria: (1) increase in serum creatinine concentration ≥ 3.8 mg/dL; (2) doubling of preoperative (baseline) serum creatinine concentration if preoperative value > 1.9 mg/dL; (3) a requirement of postoperative dialysis. Death[m] occurred within 30 days after surgery.

AKI[n] was defined as an increase in serum creatinine greater than 0.3 mg/dl or greater than 50% increase from preoperative baseline value (using RIFLE (risk, injury, failure, loss, ESRD) classification[1]).

AKI[o] was defined as an increase in serum creatinine > 0.3 mg/dl or 1.5 times or higher increase from preoperative baseline value (using RIFLE (risk, injury, failure, loss, ESRD) classification[1]) or requirement of dialysis.

AKI[i] was defined as a decrease in postoperative estimated creatinine clearance (Cockroft-Gault formula[61]) < 50 mL/min within the first 7 days after surgery; all patients had preoperative estimated creatinine clearance > 80 mL/min. Kheterpal *et al.*[26] studied only a subgroup of patients to determine the association of ACEi or ARB use with AKI.

AKI[p] was defined as an increase in serum creatinine concentration > 2.0 mg/dl within 72 hours of surgery.

Table 4: Studies: Preoperative ACEi or ARB use associated with less AKI

Author	Study Design, Setting and Patient Groups	Key Results	Conclusions	Study Limitations
Benedetto *et al.*[24]	Retrospective cohort study 536 patients who underwent cardiac surgery between 2004 and 2008 52.4% (281 out of 536) patients were on ACEi 9.1% (49 out of 536) patients developed AKI (not requiring dialysis) and 4.3% (23 out of 536) patients developed AKI-D	ACEi users vs. non-users (referent): AKI[g]: Adjusted OR = 0.48; 95% CI: 0.23 to 0.77; p = 0.04	Preoperative ACEi use may decrease the risk of AKI after cardiac surgery	Single centre study Only studied cardiac surgery Risk of overfitting in statistical model
Barodka *et al.*[23]	Retrospective cohort study 346 patients who underwent cardiac surgery between 2003 and 2007 35% (122 out of 346) patients were on ACEi or ARB 5.5% (19 out of 346) patients developed AKI and 0.9% (3 out of 346) patients developed AKI-D	ACEi or ARB users vs. non-users (referent): AKI[h]: Adjusted OR = 0.19; 95% CI: 0.04 to 0.84; p = 0.029	Preoperative ACEi or ARB may decrease the risk of AKI after cardiac surgery	Single centre study Only studied cardiac surgery Risk of overfitting in statistical model

OR: Odds ratio; CI: Confidence interval; AKI: Acute kidney injury; ACEi: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; GFR: Glomerular filtration rate; AKI-D: AKI treated with dialysis

AKI[g] was defined as a 50% or more decrease in GFR relative to preoperative baseline GFR value but not requiring dialysis and the modified diet and renal disease (MDRD) equation was used to estimate GFR.[62] Benedetto *et al.*[24] did not find significant association between preoperative ACEi use and 30-day all-cause mortality.

AKI[h] was defined with one of the following criteria: (1) increase in serum creatinine concentration above 2.0 mg/dL; (2) doubling of preoperative (baseline) serum creatinine concentration; (3) a requirement of postoperative dialysis. Barodka *et al.*[23] did not find significant association between preoperative ACEi or ARB use and 30-day all-cause mortality.

Table 5: Postoperative AKI studies: Baseline differences in ACEi or ARB users and non-users

Author	No. of patients	Baseline characteristics significantly higher in ACEi or ARB users compared to non-users (p-value < 0.05)
Kheterpal *et al.*[26]	ACEi users: 9,143; non-users: 36,148	Coronary artery disease, cerebrovascular disease, congestive heart failure, chronic obstructive pulmonary disease, diabetes mellitus, arrhythmia, hypertension, previous myocardial infarction, peripheral vascular disease, pulmonary hypertension, preoperative chronic kidney disease (serum creatinine $\geq$ 2 mg/dL), age, beta-blocker use, diuretic use, calcium channel blocker use
Miceli *et al.*[21]	ACEi users: 4,730; non-users: 4,544	Hypertension, diabetes mellitus, vascular disease, previous myocardial infarction, coronary artery disease, age
Ouzounian *et al.*[49]	ACEi users: 3,262; non-users: 2,684	Hypertension, diabetes mellitus, congestive heart failure, previous myocardial infarction, cerebrovascular disease, peripheral vascular disease, chronic kidney disease, beta-blocker use, statin use
Arora *et al.*[22]	ACEi or ARB users: 706; non-users: 652	Diabetes mellitus, hypertension, congestive heart failure, body mass index (> 25 kg/m^2)
Benedetto *et al.*[24]	ACEi users: 281; non-users: 255	Hypertension, beta-blocker use
Yoo *et al.*[28]	ACEi or ARB users: 296; non-users: 176	Diabetes mellitus, hypertension, diuretic use
Barodka *et al.*[23]	ACEi or ARB users: 122; non-users: 224	Hypertension, male gender

AKI: Acute kidney injury; ACEi: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker

CHAPTER 3 – STUDY RATIONALE AND RESEARCH QUESTIONS

3.1 Limitations of existing studies

There are several methodological limitations of the existing studies on preoperative ACEi or ARB use and postoperative AKI.[12;21-24;26-28;49;50;59;60]

(1) *Study centres*: All of the existing studies were limited to only single or two centres.

(2) *Sample size*: The results for Cittanova *et al.*[12], Arora *et al.*[22], Railton *et al*.[60] Benedetto *et al.*[24], Barodka *et al.*[23], Yoo *et al.*[28], Kincaid *et al.*[27], and Ouzounian *et al*.[49] were limited by the small sample size (249, 1358, 883, 536, 346, 472, 1209, and 1647 patients respectively). One of the concerns due to small sample size is overfitting in statistical models.[63;64] Overfitting in a statistical model occurs when it has more variables in respect to the amount of available data (e.g. A regression model requires a minimum of 10 to 12 events for every included variable to produce a stable regression model).[63;64]

(3) *Type of surgery*: With the exception of Kheterpal *et al.*[26], all of the existing studies were limited to only cardiac or vascular surgery. This raises concerns about the generalizability of the study results for other type of major surgery.

(4) *Study design*: All of the existing studies are observational in nature and could not establish the causal association between preoperative ACEi or ARB use and postoperative AKI.[65]

3.2 Choice of study design

The best estimates for treatment effects come from randomized controlled trials (RCT).[65] However, a limitation to conducting such a trial on the outcome of AKI-D is one of logistics and cost.

For example, a sample size of over 156,500 patients is needed to conduct an RCT on the outcome of AKI-D. (Assumptions: i) incidence of AKI-D of 0.45% in a group of patients having any type of major surgery, ii) 1:1 allocation (ACEi or ARB users vs. non-users), iii) relative risk reduction of 20% with ACEi or ARB use, iv) no loss to follow-up, v) two tailed $\alpha = 0.05$, and vi) $1 - \beta = 0.8$). It would not be possible to conduct such a large RCT.

On the other hand, well designed cohort studies can provide useful information on estimates of treatment effects, and can guide the conduct and interpretation of future RCT.[65] For this reason, we conducted a population based retrospective cohort study in Ontario, Canada to determine whether preoperative ACEi or ARB use compared to non-use is associated with an increased risk of AKI-D following a non-urgent major surgical procedure.

3.3 Research Questions

3.3.1 Primary research question

In elderly patients undergoing non-urgent major surgery:

Is preoperative ACEi or ARB use (vs. non-use) associated with a higher risk of postoperative AKI-D?

Hypothesis: Preoperative ACEi or ARB use increases the risk of AKI-D compared to non-use.

3.3.2 Secondary research question

In elderly patients undergoing non-urgent major surgery:

Is preoperative ACEi or ARB use (vs. non-use) associated with an increased risk of postoperative all-cause mortality?

Hypothesis: Preoperative ACEi or ARB use increases the risk of all-cause mortality compared to non-use.

CHAPTER 4 – STUDY METHODS

4.1 Study overview and setting

We performed a *retrospective cohort study* of elderly patients in the province of Ontario, Canada who were admitted to a hospital for a non-urgent, elective surgical procedure. We performed this study in accordance with a prespecified study protocol approved by the institutional review board (IRB) of Sunnybrook Health Sciences Centre, Toronto (detailed data creation plan in Appendix A). We used several linked Ontario health administrative databases held at ICES (Institute for Clinical Evaluative Sciences). We followed guidelines as stated in STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) to report the findings of our study (detailed in Appendix B).[66]

4.2 Data Sources

All the residents in Ontario (Canada) have universal coverage for health-care services under the Ontario Health Insurance Plan (OHIP).[17] Moreover, the Ontario Drug Benefits (ODB) plan covers routinely prescribed outpatient medications for patients 65 years of age or older.[17] Patients' related health information such as vital status, demographics, outpatient health-care access, hospitalization, procedures (such as therapeutic, diagnostic, surgical procedures etc.), and drug prescriptions are electronically collected in several health administrative databases.[17] The Institute for Clinical Evaluative Sciences has anonymously linked these databases for the purposes of population based health research.[17;67-75]

We used the following databases in our study:

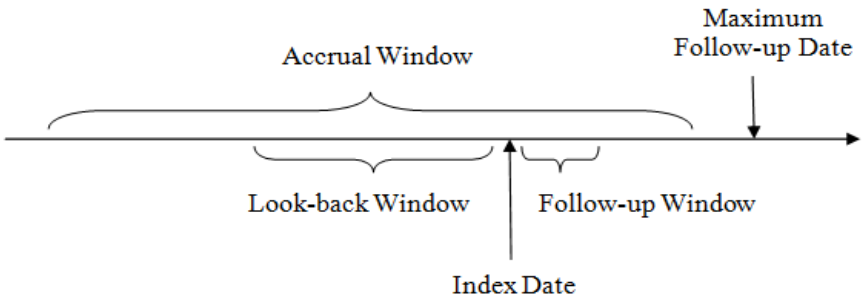
(1) Ontario Drug Benefits (ODB) Database: We reviewed the ODB database from September 1994 to November 2010 to obtain information on different outpatient medications such as drug identification number (DIN), therapeutic class etc.[17] There was a minimal error rate of 0.7% (95% CI: 0.5% to 0.9%) on prescriptions dispended within this database.[72]

(2) Canadian Institute for Health Information (CIHI) – Discharge Abstract Database (DAD): The CIHI-DAD collects information on hospital admissions including demographic and procedural information such as therapeutic, diagnostic, and surgical procedures.[17] The CIHI-DAD used the Canadian Modified International Classification of Disease ninth version (ICD-9 CA) before 2002 and ICD-10 CA (10^{th} version) thereafter. We reviewed the CIHI-DAD from January 1992 to November 2010 to obtain various patients' related health information.

(3) Ontario Health Insurance Plan (OHIP) Database: The OHIP database records information on billing claims for inpatient, outpatient, and laboratory services.[17] We reviewed the OHIP database from January 1992 to February 2011.

(4) Registered Persons Database (RPDB): The RPDB provides information on demographics and vital statistics such as vital status, socioeconomic status, birth-date, sex, and postal code for the residents in Ontario.[17] We reviewed the RPDB from January 1992 to February 2011.

Table 6: Time Frame Definitions



Accrual start date	January 1, 1995
End date	November 30, 2010
Maximum follow-up date	90 days after index date (February 28, 2011)
When did follow-up window terminate?	Whichever came first: a) death; or b) 90 days after index date
Look-back window(s) from index date	3 years for comorbid conditions 120 days for ODB medications

4.3 Patients

We selected patients' over the age of 66 years who were admitted to a hospital in Ontario (Canada) for an elective, non-urgent surgical procedure between January 1, 1995 and November 30, 2010. Patients age 65 years or older receive universal prescription coverage under ODB plan in Ontario. Patients who were in their first year of coverage (age 65 years) were excluded to avoid incomplete medication records. We studied the following five surgical categories which all carry an appreciable risk for the complication of AKI-D[4;17;20]: 1) Cardiac; 2) Thoracic; 3) Vascular; 4) Abdominal; and 5) Retro-peritoneal (bladder, ureter, kidney).

We defined the 'index date' as the date of elective, non-urgent surgical procedure during a hospital admission. If there was a missing procedural date, we used the hospital admission date.

We excluded all the surgeries done during the course of a non-surgical hospital admission to avoid selecting emergent or urgent surgery. We also excluded one hospital from analysis where a single treatment of intra-operative dialysis was routinely performed upon patients undergoing cardiopulmonary bypass surgery.

In a data cleaning step, we excluded hospital admissions associated with invalid or a missing provincial health card number (ICES key number), missing age or sex, or any records with errors in vital statistics (< 1.2% of records excluded for these reasons). We limited our analyses to patients with at least one ODB prescription in the 120 days prior to the index date to ensure patients were assessing the ODB plan before surgery and were in Ontario. In order to assess of the event of new postoperative AKI-D, we excluded patients with any evidence of dialysis or kidney transplantation in the 3 years prior to surgery.

To avoid the need to account for less frequently prescribed anti-hypertensive medications in the analysis, we only considered those patients who could have evidence of a prescription for the following frequently prescribed anti-hypertensive medications in the 120 days prior to surgery: ACEi, ARB, beta-adrenergic blocker, calcium channel blocker, non-potassium sparing diuretic (loop diuretic and thiazide diuretic), and excluded remaining anti-hypertensive medications. For patients with multiple eligible surgical procedures during the study period, we selected one surgical procedure at random and excluded the remaining procedures to avoid within patient clustering in the analysis.

4.4 Preoperative ACEi or ARB use

Within our study, our exposure group contained ACEi or ARB users, if there was evidence of at least one ODB prescription for an ACEi or ARB in the 120 days prior to the index date. Non-users (control group) had no evidence of an ODB prescription for an ACEi or ARB in the 120 days prior to the index date. We considered a time frame of 120 days because the ODB plan requires that each prescription be renewed at least every 100 days and we added 20 extra days to accommodate missed doses.[76]

4.5 Baseline Characteristics

We evaluated demographic characteristics and comorbidities for selected patients using validated database codes whenever possible (provided in Appendix C).[17;77-85] We also evaluated concomitant medications use in the 120 days prior to the index date.

4.6 Potential Confounders

We considered factors associated with ACEi or ARB use and those associated with postoperative AKI to determine potential confounders.[4;11-13;17;20-28;30;49;50;59;60;86] We adjusted for the following potential confounders in the logistic regression analysis: age (in years), sex (male/female; referent = female), chronic obstructive pulmonary disease (yes/no; referent = no), cerebrovascular disease (yes/no; referent = no), peripheral vascular disease (yes/no; referent = no), coronary artery disease (yes/no; referent = no), congestive heart failure (yes/no; referent = no), chronic kidney disease (yes/no; referent = no), chronic liver disease (yes/no; referent = no), antidiabetic agent (yes/no; referent = no), beta-adrenergic blocker (yes/no; referent = no), calcium channel blocker (yes/no; referent = no), non-potassium sparing diuretic

(yes/no; referent = no), statin (yes/no; referent = no), type of surgery (cardiac, thoracic, vascular, abdominal, retro-peritoneal; referent = abdominal), era of surgery (1995 to 1998, 1999 to 2001, 2002 to 2004, 2005 to 2007, 2008 to 2010; referent = 1995 to 1998)

4.7 Primary and secondary outcomes

The primary outcome was AKI-D within 14 days of the index date. We assessed the primary outcome of AKI-D using OHIP database codes for acute dialysis (provided in Appendix D).[17;87] The secondary outcome was all-cause mortality within 90 days of the index date.

4.8 Primary Analysis

Statistical analysis was performed using SAS 9.2 (SAS Institute, Cary, NC, USA). We evaluated differences in baseline characteristics between ACEi or ARB users and non-users using standardized differences and considered > 10% as a meaningful difference between the two groups.[86] For our primary and secondary outcomes, we determined the total number of events for ACEi or ARB users and non-users followed by unadjusted and adjusted logistic regression analysis with non-users as the referent group. We determined the unadjusted odds ratio (OR), the adjusted OR, and their 95% confidence intervals (CI). We adjusted for all the prespecified potential confounders in the logistic regression analysis to determine the adjusted OR. Given the low observed incidence for our study outcomes, we interpreted odds ratios as relative risks.[88]

4.9 Additional Analyses

We conducted several additional analyses to explore the relationship between preoperative ACEi or ARB use and outcomes.

(1) *Propensity score matching*: Cohort studies are prone to selection bias that might predispose a patient to receive or not receive ACEi or ARB prior to surgery.[86;89-91] Because of this form of bias, cohort studies may be limited in their ability to make comparisons between ACEi or ARB users and non-users.[86;89-91] A propensity score matched analysis is a statistical approach to reduce this form of bias.[89-91] In our context, we analyzed numerous risk factors that were associated with why a patient was or was not prescribed preoperative ACEi or ARB and assigned a propensity score – this score indicated the likelihood of ACEi or ARB use if the risk factor was present.[86;89-91] When multiple risk factors were present in a single patient, we amalgamated the propensity scores for those risk factors and assigned an overall propensity score for that patient from 0 to 1 reflecting the likelihood of receiving ACEi or ARB.[89] We then matched patients receiving preoperative ACEi or ARB on one-to-one basis with patients not receiving ACEi or ARB who had an identical overall propensity score.[89] We excluded patients not successfully matched through this process.[89]

In our study we performed an individual one-to-one match based on age (± 5 years), sex (men/women) and the presence of chronic kidney disease (yes/no). We then derived a propensity score for every patient from all the potential confounders prespecified in our logistic regression analysis and matched each

ACEi or ARB user to a non-user using a caliper of ± 0.2 standard deviation of all the propensity scores.[89] Through this process we obtained a group of matched cohort for ACEi or ARB users and non-users.[89] Each non-user could only be selected once to derive the propensity score. For the primary and secondary outcomes, we determined the total number of events for propensity matched ACEi or ARB users and non-users followed by relative risk (95% CI). We also calculated absolute risk reduction (95% CI) for primary and secondary outcomes.[88] In a case where preoperative ACEi or ARB use was beneficial, we calculated the number needed to treat (1 / absolute risk reduction), which indicates how many patients need to receive preoperative ACEi or ARB to prevent one patient from developing an event such as receipt of AKI-D who otherwise would have developed the event (a lower number indicating a more beneficial effect of ACEi or ARB use).[88]

(2) *Effect modification by preoperative chronic kidney disease, era of surgery, and type of surgery:* We performed subgroup analyses (tests of effect modification) for the outcome of AKI-D and all-cause mortality for the following three characteristics: presence of preoperative chronic kidney disease (yes/no), era of surgery (1995 to 1998, 1999 to 2001, 2002 to 2004, 2005 to 2007, 2008 to 2010), and type of surgery (cardiac, thoracic, vascular, abdominal, retro-peritoneal). We fit a logistic regression model to perform subgroup analyses where we adjusted for all the prespecified potential confounders except the subgroup factor being tested. We determined the total number of events and event rate per 10,000 persons followed by the

unadjusted and adjusted relative risk (95% CI). We considered a p-value < 0.05 for the test of effect modification to be significant.

(3) *Time to event analysis*: We repeated our analysis using a Cox-proportional hazards model for the outcome of AKI-D, censored for death or end of the 14th day after index date. We adjusted for all prespecified potential confounders and determined the adjusted hazard ratio (95% CI) for ACEi or ARB users with non-users as the referent group.

CHAPTER 5 – STUDY RESULTS

5.1 Baseline characteristics: ACEi or ARB users and non-users

We identified 237,208 patients from 118 hospitals in Ontario (Canada) after applying our selection criteria (Figure 3). There were 101,494 (42.8%) ACEi or ARB users and 135,714 (57.2%) non-users. The baseline characteristics for ACEi or ARB users and non-users are presented in Table 7. In comparison to non-users, ACEi or ARB users were more likely to be male, were on a higher number of medications such as anti-diabetic agent, other anti-hypertensive medications (beta-blocker, calcium channel blocker, and non-potassium sparing diuretic) and statin, had higher rates of cerebrovascular disease, peripheral vascular disease, coronary artery disease including angina, congestive heart failure, and chronic kidney disease. ACEi or ARB users were more likely to undergo cardiac and vascular surgeries compared to other types of eligible surgeries. Patients having their surgery in more recent years (2002 to 2010) were more likely to have received preoperative ACEi or ARB compared to past years (1995 to 2001).

5.2 Primary analysis: AKI-D and all-cause mortality

The incidence of postoperative AKI-D (within 1 to 14 days after surgery) was 0.34% (810 out of 237,208 patients) and postoperative 90-day all-cause mortality was 4.67% (11,089 out of 237,208 patients). After adjustment for prespecified potential confounders, ACEi or ARB use prior to surgery was associated with a lower relative risk of AKI-D (adjusted relative risk (RR): 0.83; 95% CI: 0.71 to 0.98) and a lower relative risk of 90-day all-cause mortality (adjusted RR: 0.91; 95% CI: 0.87 to 0.95) (Table 8).

5.3 Additional Analyses

5.3.1 Propensity score matched analysis: AKI-D and all-cause mortality

Out of 101,494 ACEi or ARB users selected for the primary analysis, 67,822 ACEi or ARB users were matched to 67,822 non-users using predefined characteristics including the propensity score (Table 7). Similar to the primary analysis, preoperative ACEi or ARB use was associated with a lower relative risk of AKI-D (RR: 0.77; 95% CI: 0.65 to 0.92) and a lower relative risk of 90-day all-cause mortality (RR: 0.93; 95% CI: 0.88 to 0.97) (Table 9). For the outcome of AKI-D, the absolute risk reduction (ARR) for ACEi or ARB users compared to non-users was 0.09% and number needed to treat (NNT) was 1,077. It indicates that 1,077 patients need to be treated with ACEi or ARB prior to surgery to prevent one case of postoperative AKI-D. Similarly, for the outcome of 90-day all-cause mortality, the ARR for ACEi or ARB users compared to non-users was 0.35%, and the NNT was 289.

5.3.2 Subgroup analysis for AKI-D and all-cause mortality

We summarized the results for subgroup analysis for AKI-D and all-cause mortality in Table 10 and Table 11. We did not find type of surgery or era of surgery modified the association between preoperative ACEi or ARB use and AKI-D. For patients with chronic kidney disease, we observed a lower incidence of AKI-D (246.8 per 10,000 persons) in preoperative ACEi or ARB users compared to non-users (354.1 per 10,000 persons). Preoperative ACEi or ARB use in patients with chronic kidney disease was associated with a lower relative risk of AKI-D (adjusted RR: 0.62; 95% CI: 0.50 to 0.78), while there was no such association in patients without chronic kidney disease (adjusted RR: 1.00; 95% CI: 0.81 to 1.24), with a significant test of interaction by the

presence of chronic kidney disease (p-value < 0.0001). We did not find significant effect modification by chronic kidney disease, type of surgery, or era of surgery on the outcome of all-cause mortality.

5.3.3 Time to event analysis for AKI-D

We observed similar result in the time to event analysis for AKI-D. The adjusted hazard ratio for preoperative ACEi or ARB use compared to non-use was 0.83 (95% CI: 0.71 to 0.97).

Figure 3: Flow diagram: Patient selection

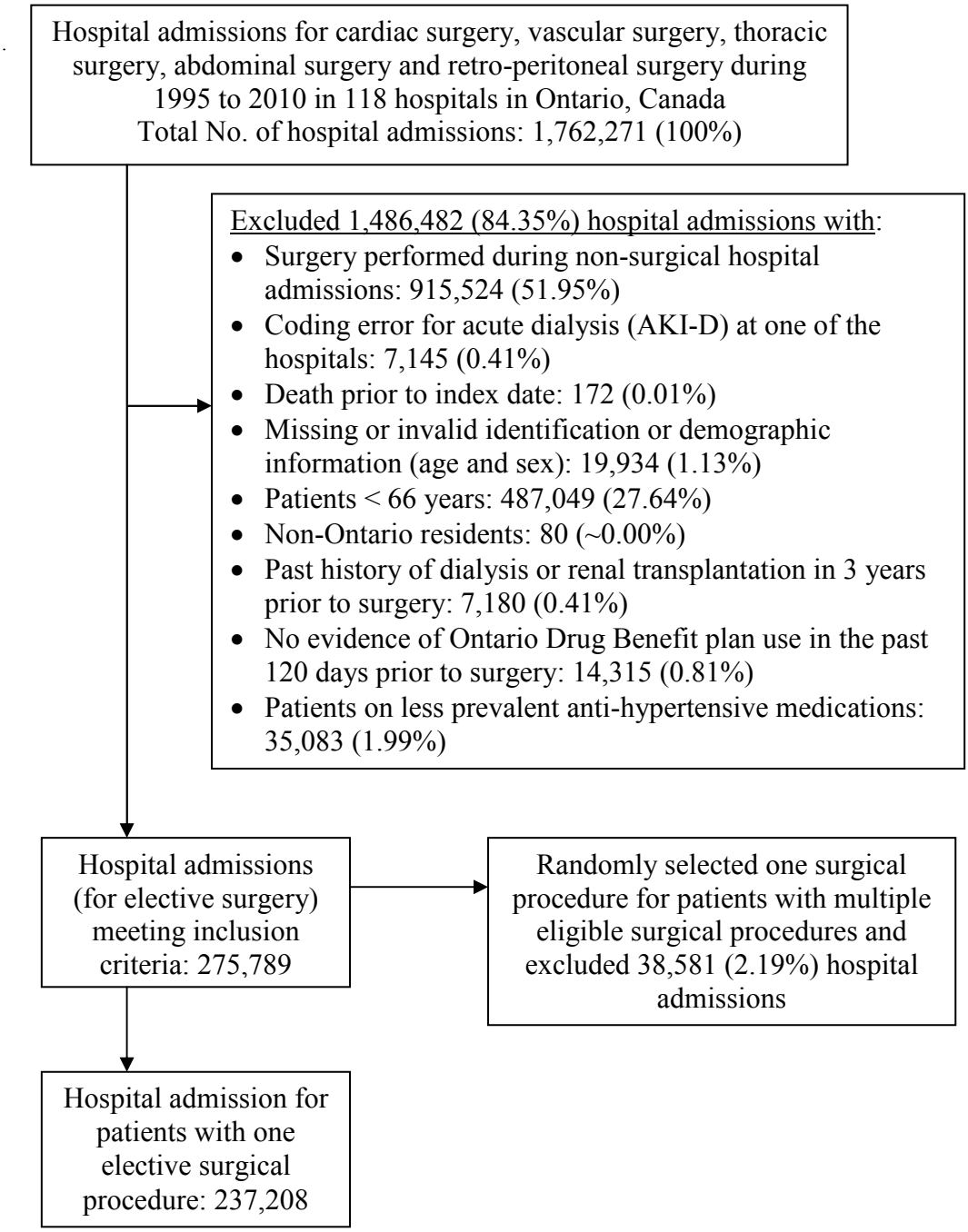


Table 7: Baseline characteristics: ACEi or ARB users and non-users

	Entire Cohort			Propensity Matched Cohort	
	ACEi or ARB users	**Non-users (control)**		**ACEi or ARB users**	**Non-users (control)**
	N=101,494	**N=135,714**		**N=67,822**	**N=67,822**
Demographics					
Age at index date (years)	74 (70 to 78)	73 (69 to 78)		74 (70 to 78)	74 (70 to 78)
Age groups (years)					
66 to 70	30,557 (30.1%)	43,652 (32.2%)		20,098 (29.6%)	20,165 (29.7%)
71 to 75	30,966 (30.5%)	40,782 (30.0%)		20,482 (30.2%)	20,391 (30.1%)
76 to 80	23,898 (23.5%)	29,529 (21.8%)		15,982 (23.6%)	15,779 (23.3%)
81 to 85	11,812 (11.6%)	15,361 (11.3%)		8,101 (11.9%)	8,205 (12.1%)
86 to 90	3,651 (3.6%)	5,294 (3.9%)		2,682 (4.0%)	2,761 (4.1%)
91+	610 (0.6%)	1,096 (0.8%)		477 (0.7%)	521 (0.8%)
Women	41,034 (40.4%)	60,522 (44.6%)		29,425 (43.4%)	29,425 (43.4%)
Comorbidities					
Chronic obstructive pulmonary disease	5,806 (5.7%)	7,121 (5.2%)		3,789 (5.6%)	3,527 (5.2%)
Cerebrovascular disease	18,016 (17.8%)*	17,551 (12.9%)*		10,970 (16.2%)	11,097 (16.4%)
Peripheral vascular disease	6,490 (6.4%)*	5,571 (4.1%)*		3,675 (5.4%)	3,599 (5.3%)
Coronary artery disease	67,921 (66.9%)*	61,137 (45.0%)*		40,114 (59.1%)	40,346 (59.5%)
Congestive heart failure	22,108 (21.8%)*	12,413 (9.1%)*		10,740 (15.8%)	10,317 (15.2%)
Chronic kidney disease	7,538 (7.4%)*	5,027 (3.7%)*		3,852 (5.7%)	3,852 (5.7%)
Chronic liver disease	295 (0.3%)	478 (0.4%)		200 (0.3%)	194 (0.3%)
Medications					
Oral hypoglycemic	21,267 (21.0%)*	10,381 (7.6%)*		8,766 (12.9%)	8,625 (12.7%)

Insulin	6,089 (6.0%)*	2,381 (1.8%)*		2,348 (3.5%)	1,937 (2.9%)
Anti-diabetic agent	25,041 (24.7%)*	12,215 (9.0%)*		10,364 (15.3%)	10,076 (14.9%)
Beta-adrenergic blocker	44,835 (44.2%)*	34,096 (25.1%)*		24,550 (36.2%)	24,702 (36.4%)
Calcium channel blocker	36,659 (36.1%)*	32,859 (24.2%)*		21,630 (31.9%)	22,131 (32.6%)
Non-potassium sparing diuretic	40,345 (39.8%)*	22,042 (16.2%)*		19,830 (29.2%)	19,595 (28.9%)
Statin	53,915 (53.1%)*	31,691 (23.4%)*		27,348 (40.3%)	26,913 (39.7%)
Surgical Characteristics					
Type of Surgery					
Cardiac surgery	40,694 (40.1%)*	29,475 (21.7%)*		22,222 (32.8%)	22,380 (33.0%)
Thoracic surgery	5,771 (5.7%)	10,177 (7.5%)		4,561 (6.7%)	4,176 (6.2%)
Vascular surgery	18,459 (18.2%)*	18,969 (14.0%)*		11,509 (17.0%)	11,904 (17.5%)
Abdominal surgery	30,471 (30.0%)*	64,911 (47.8%)*		24,592 (36.2%)	24,630 (36.3%)
Retro-peritoneal surgery	6,099 (6.0%)*	12,182 (9.0%)*		4,938 (7.3%)	4,732 (7.0%)
Era of surgery					
1995 to 1998	14,718 (14.5%)*	45,173 (33.3%)*		13,278 (19.6%)	13,647 (20.1%)
1999 to 2001	16,900 (16.6%)*	30,122 (22.2%)*		13,457 (19.8%)	13,963 (20.6%)
2002 to 2004	20,960 (20.7%)*	21,992 (16.2%)*		13,404 (19.8%)	13,194 (19.5%)
2005 to 2007	23,711 (23.4%)*	19,520 (14.4%)*		13,625 (20.1%)	13,300 (19.6%)
2008 to 2010	25,205 (24.8%)*	18,907 (13.9%)*		14,058 (20.7%)	13,718 (20.2%)

ACEi: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker

Data are presented as number (percentage (rounding off to one decimal place)) with the exception of age at index date. Age at index date is presented as median (interquartile range). Index date is a surgical procedure date or a hospital admission date (if the surgical procedure date is not available).

*Represents a standardized difference of > 10% between ACEi or ARB users and non-users. We considered a standardized difference of > 10% between ACEi or ARB users and non-users as a meaningful difference.[86] Standardized differences are not much sensitive to sample size compared to traditional hypothesis tests.[86] It is calculated by examining the difference between ACEi or ARB users and non-users divided by the pooled standard deviation of the two groups.[86]
A total of 3% (3,091 out of 101,494) patients were on both ACEi and ARB medication.

Table 8: Association between preoperative ACEi or ARB use and outcomes

Outcomes	No. of patients with event (percent)		Relative Risk (95% Confidence Interval)	
	ACEi or ARB users (N=101,494)	Non-users (N=135,714)	Unadjusted	Adjusted*
AKI-D (1 to 14 days after surgery)	438 (0.43%)	372 (0.27%)	1.58 (1.37, 1.81)	0.83 (0.71, 0.98)
Death (1 to 90 days after surgery)	4,654 (4.59%)	6,435 (4.74%)	0.97 (0.93, 1.00)	0.91 (0.87, 0.95)

ACEi: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; AKI-D: Acute kidney injury treated with dialysis

Relative risk was calculated for preoperative ACEi or ARB use compared to non-use

*Adjusted for age, sex, chronic obstructive pulmonary disease, cerebrovascular disease, peripheral vascular disease, coronary artery disease, congestive heart failure, chronic kidney disease, chronic liver disease, anti-diabetic agent, beta-adrenergic blocker, calcium channel blocker, non-potassium sparing diuretic, statin, type of surgery (cardiac, thoracic, vascular, abdominal, retro-peritoneal), era of surgery (1995-1998, 1999-2001, 2002-2004, 2005-2007, 2008-2010)

Table 9: Propensity score matched analysis: Preoperative ACEi or ARB use and outcomes

Outcomes	No. of patients with event (percent)		Relative Risk (95% CI)	Absolute Risk Reduction (95% CI)	Number Needed to Treat[+]
	ACEi or ARB users	Non-users			
	(N=67,822)	(N=67,822)			
AKI-D (1 to 14 days after surgery)	215 (0.32%)	278 (0.41%)	0.77 (0.65, 0.92)	0.09% (0.03%, 0.16%)	1,077
Death (1 to 90 days after surgery)	3,060 (4.51%)	3,295 (4.86%)	0.93 (0.88, 0.97)	0.35% (0.12%, 0.57%)	289

ACEi: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; AKI-D: Acute kidney injury treated with dialysis; CI: Confidence interval

Relative risk was calculated for preoperative ACEi or ARB use compared to non-use

[+]The number needed to treat is the reciprocal of the absolute risk reduction (1 / absolute risk reduction) and indicates the total number of patients who need to be treated with an ACEi or ARB prior to surgery to prevent one case of AKI-D or death, respectively.[88]

Table 10: Subgroup analysis for AKI-D

	No. of events		Event rate per 10,000 persons		Relative Risk (95% Confidence Interval)		P-value (Test for interaction)
	ACEi or ARB users	Non-users	ACEi or ARB users	Non-users	Unadjusted	Adjusted[+]	
CKD							
Yes	186 / 7,538	178 / 5,027	246.75	354.09	0.69 (0.56, 0.85)	0.62 (0.50, 0.78)	< 0.0001
No	252 / 93,956	194 / 130,687	26.82	14.84	1.81 (1.50, 2.18)	1.00 (0.81, 1.24)	
Era of surgery							
1995 to 1998	77 / 14,718	113 / 45,173	52.32	25.01	2.10 (1.57, 2.80)	1.13 (0.81, 1.56)	NS
1999 to 2001	57 / 16,900	68 / 30,122	33.73	22.57	1.50 (1.05, 2.13)	0.78 (0.53, 1.15)	
2002 to 2004	93 / 20,960	66 / 21,992	44.37	30.01	1.48 (1.08, 2.03)	0.88 (0.62, 1.25)	
2005 to 2007	92 / 23,711	63 / 19,520	38.80	32.27	1.20 (0.87, 1.66)	0.64 (0.45, 0.92)	
2008 to 2010	119 / 25,205	62 / 18,907	47.21	32.79	1.44 (1.06, 1.96)	0.84 (0.60, 1.17)	
Type of surgery							
Cardiac	232 / 40,694	147 / 29,475	57.01	49.87	1.14 (0.93, 1.41)	0.74 (0.59, 0.93)	NS
Thoracic	14 / 5,771	12 / 10,177	24.26	11.79	2.06 (0.95, 4.46)	1.84 (0.77, 4.40)	
Vascular	117 / 18,459	92 / 18,969	63.38	48.50	1.31 (0.99, 1.72)	1.09 (0.80, 1.48)	
Abdominal	71 / 30,471	109 / 64,911	23.30	16.79	1.39 (1.03, 1.87)	0.72 (0.52, 1.01)	
Retro-peritoneal	4 / 6,099	12 / 12,182	6.56	9.85	0.67 (0.22, 2.07)	0.94 (0.28, 3.22)	

AKI-D: Acute kidney injury treated with dialysis; ACEi: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; CKD: Chronic kidney disease; NS: not significant;

Relative risk was calculated for preoperative ACEi or ARB use compared to non-use

[+] For adjusted analyses, we included all the prespecified potential confounders except the subgroup factor being tested

Table 11: Subgroup analysis for all-cause mortality

	No. of events		Event rate per 10,000 persons		Relative Risk (95% Confidence Interval)		P-value (Test for interact-ion)
	ACEi or ARB users	Non-users	ACEi or ARB users	Non-users	Unadjusted	Adjusted[+]	
CKD							
Yes	606 / 7,538	467 / 5,027	803.93	928.98	0.85 (0.75, 0.97)	0.86 (0.75, 0.98)	} NS
No	4,048 / 93,956	5,968 / 130,687	430.84	456.66	0.94 (0.90, 0.98)	0.91 (0.87, 0.96)	
Era of surgery							
1995 to 1998	846 / 14,718	2,077 / 45,173	574.81	459.79	1.27 (1.17, 1.37)	1.05 (0.95, 1.15)	} NS
1999 to 2001	790 / 16,900	1,418 / 30,122	467.46	470.75	0.99 (0.91, 1.09)	0.96 (0.87, 1.06)	
2002 to 2004	922 / 20,960	1,089 / 21,992	439.89	495.18	0.88 (0.81, 0.97)	0.87 (0.79, 0.96)	
2005 to 2007	1,005 / 23,711	967 / 19,520	423.85	495.39	0.85 (0.78, 0.93)	0.81 (0.74, 0.90)	
2008 to 2010	1,091 / 25,205	884 / 18,907	432.85	467.55	0.92 (0.84, 1.01)	0.90 (0.82, 0.99)	
Type of surgery							
Cardiac	1,460 / 40,694	1,184 / 29,475	358.78	401.69	0.89 (0.82, 0.96)	0.82 (0.75, 0.89)	} NS
Thoracic	432 / 5,771	830 / 10,177	748.57	815.56	0.91 (0.81, 1.03)	1.00 (0.87, 1.15)	
Vascular	936 / 18,459	916 / 18,969	507.07	482.89	1.05 (0.96, 1.16)	1.02 (0.91, 1.13)	
Abdominal	1,625 / 30,471	3,112 / 64,911	533.29	479.43	1.12 (1.05, 1.19)	0.92 (0.86, 0.99)	
Retro-peritoneal	201 / 6,099	393 / 12,182	329.56	322.61	1.02 (0.86, 1.23)	0.92 (0.76, 1.13)	

ACEi: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; CKD: Chronic kidney disease; NS: not significant;

Relative risk was calculated for preoperative ACEi or ARB use compared to non-use

[+] For adjusted analyses, we included all the prespecified potential confounders except the subgroup factor being tested

CHAPTER 6 – GENERAL DISCUSSION

6.1 Summary of study results

The benefits of chronic ACEi or ARB use in reducing cardiovascular morbidity and mortality have been established in several international randomized controlled trials.[32-38] However, optimal ACEi or ARB use in the perioperative period is still a matter of debate and practice patterns vary on whether these medications should be used or temporarily held prior to surgery.[21;22;40-42;51-53]

We conducted a large population based retrospective cohort study to determine whether ACEi or ARB use prior to elective surgery is associated with a higher risk of AKI-D. Contrary to our hypothesis, ACEi or ARB use prior to surgery was associated with 17% lower relative risk of AKI-D and 9% lower relative risk of 90-day all-cause mortality after adjusting for relevant baseline characteristics. We observed similar results with propensity score matched analyses. However, we observed a significant effect modification by chronic kidney disease on AKI-D and the benefit of preoperative ACEi or ARB use in reducing the risk of AKI-D was only observed in patients with chronic kidney disease.

6.2 Interpreting study results

There is a supporting biological rationale which explains why ACEi or ARB use may improve outcomes in the perioperative setting. Both ACEi and ARB reduce the activity of angiotensin II which is thought to result in kidney protection.[25;30;45-48] There are at least four potential mechanisms by which angiotensin II may increase the risk of postoperative AKI and mortality: i) Angiotensin II is a potent vasoconstrictor and acts

directly on the renal efferent arteriole, severely altering renal hemodynamics, ii) it increases super oxide anion production and can lead to oxidative stress and impaired endothelial function, iii) it can accelerate the inflammatory response by promoting release of inflammatory mediators, adhesion molecules, and proinflammatory transcription factors, and iv) it accelerates acute ischemic events by increasing the release of plasminogen activator inhibitor-1.[25;30;45-48] By reducing the activity of angiotensin II, ACEi or ARB may prevent the aforementioned events from increasing risk of kidney damage and death.[25;30;45-48]

Our results are consistent with two previous small studies (studies summarized in Table 3). Benedetto *et al*.[24] studied 536 patients who underwent cardiac surgery and noted that preoperative ACEi use compared to non-use was associated with a lower risk of postoperative AKI (adjusted OR: 0.48; 95% CI: 0.23 to 0.77). The authors speculated the pathophysiologic benefit of ACEi use stemmed from preservation of renal blood flow during surgery.[24] Following 346 patients who underwent cardiac surgery, Barodka *et al*.[23] observed that preoperative ACEi or ARB use compared to non-use was associated with a substantially lower risk of AKI (adjusted OR: 0.19; 95% CI: 0.04 to 0.84). Contrary to our results, neither Benedetto *et al*.[24] or Barodka *et al*.[23] found a statistically significant association between preoperative ACEi or ARB use and all-cause mortality.

Miceli *et al*.[21] performed a propensity score matched analysis in 9,274 patients who underwent cardiac surgery and observed that preoperative ACEi use compared to non-use was associated with a 1.36 fold higher risk of postoperative AKI (adjusted OR: 1.36; 95% CI: 1.10 to 1.67) and a two-fold higher risk of postoperative mortality

(adjusted OR: 2.00; 95% CI: 1.17 to 3.42). Miceli *et al*.[21] suggested that postoperative AKI occurred as a result of decreased renal perfusion, mainly due to decreased arterial pressure along with increased intraoperative use of vasoconstrictors.

An additional four epidemiological studies conducted by Ouzounian *et al*.[49], Rady *et al*.[50], Yoo *et al.*[28], and Barodka *et al.*[59] (studies summarized in Table 4), demonstrated no significant association between preoperative ACEi or ARB use and postoperative AKI. However, all the four studies observed a non-significant trend towards benefit with preoperative ACEi or ARB use (adjusted OR < 1.00; p-value: not significant) and these could have been due to insufficient statistical power to detect a meaningful clinical benefit.[28;49;50;59]

The major considerations in comparing our study results with all previous studies are the heterogeneous AKI definitions and type of surgery studied.[12;21-24;26-28;49;50;59;60] We studied the outcome of AKI-D, the renal outcome most important to patients and their health-care providers.[92] It differs from an outcome of AKI defined by acute changes in serum creatinine.[1;5] The latter is a surrogate outcome, and could be misleading particularly in the ACEi or ARB use setting (i.e. ACEi or ARB use versus placebo may increase serum creatinine concentration but prevents the most clinically important renal outcome of end-stage renal disease requiring on-going maintenance dialysis).[22;25;29;30;44] Out of all previous studies on this issue[12;21-24;26-28;49;50;59;60], only Railton *et al*.[60] studied the outcome of AKI-D and observed a higher risk for AKI-D with preoperative ACEi or ARB use (summarized in Table 2). However, the study was limited by a small group of patients (883 patients) who underwent abdominal aortic aneurysm (AAA) repair and a small number of AKI-D events (24 events).[60]

Contrary to our study and Railton *et al*.[60], the remaining studies defined AKI using different criteria[12;21-24;26-28;49;50;59], such as: i) a composite outcome on changes in serum creatinine and AKI-D, ii) changes in serum creatinine using RIFLE classification[1], iii) changes in serum creatinine using arbitrary criteria, iv) changes in creatinine clearance or glomerular filtration rate (AKI definitions provided in footnotes of Table 2, 3, and 4). Different from our study and Kheterpal *et al.*[26], all existing previous studies considered only cardiac or vascular surgery to examine the association with postoperative AKI.[12;21-24;27;28;49;50;59;60] However, Kheterpal *et al.*[26], after applying their selection criteria of overnight hospital admission, no urological procedure, and normal preoperative renal function, only studied a subgroup of patients (3,256 patients) out of a large cohort (45,291 patients) who underwent non-cardiac surgery. Kheterpal *et al.*[26] observed no significant association between preoperative ACEi or ARB use and postoperative AKI and surmised this was potentially due to the limited small sample size.

Although we observed a lower relative risk of AKI-D with preoperative ACEi or ARB use, the benefit was only seen in patients with chronic kidney disease, while we found no significant association in patients without chronic kidney disease. Chronic kidney disease is considered to be the most important risk factor for AKI.[13;20] However, majority of the previous studies did not account for chronic kidney disease in their analyses, so we do not know whether this explains differences in study results.[12;21-24;26-28;49;50;59;60]

6.3 Study Strengths

Our study has a number of strengths:

(1) The large sample size (237,208 patients) from 118 hospitals in Ontario increased the generalizability of the study results.

(2) Statistical overfitting with poor regression modeling can occur when there are less than 10 to 12 events for every variable included in the regression analysis.[63;64] Unlike other studies, the large number of events for the primary outcome in our study (AKI-D, 810 events) reduced concerns about statistical overfitting.[23;24;63;64]

(3) To the best of our knowledge, this is the largest cohort study to examine the association between preoperative ACEi or ARB use and postoperative AKI.

(4) AKI prevention is important for both cardiac and non-cardiac major surgeries. This is first study of its kind that considered both cardiac and non-cardiac major surgeries (including thoracic, vascular, abdominal and retro-peritoneal surgeries).

(5) Given there were less than 1% yearly emigration from Ontario, the loss to follow up was minimal.[93]

(6) The information in Ontario health administrative databases reflects routine clinical practice and therefore, less prone to screening biases that could arise in other types of studies.[17;70;71;73]

(7) Our data sources provided accurate information on the dispensing of different outpatient medication prescriptions with a minimal error rate of 0.7% (95% CI: 0.5% to 0.9%).[72]

6.4 Study Limitations

The study does have some limitations:

(1) Confounding by indication, due to non random allocation of treatment, is well described in observational studies related to pharmacoepidemiology.[89-91] Because of this issue, the associations observed in this study may not be causal.[89-91] In other words, it is possible the results observed in this study are attributable to residual confounding rather than a true ACEi or ARB effect.[90;91;94;95] Patients with comorbidities such as chronic kidney disease, diabetes, hypertension, congestive heart failure, coronary artery disease, and peripheral vascular disease are more likely to receive an ACEi or ARB, and these comorbidities also increase the risk for AKI.[4;11;13;20;21;25;26] To deal with confounding, we adjusted for potential confounders in logistic regression analysis.[89-91;95] We also repeated our analysis using propensity score matching.[89-91;95] It is reassuring that these different methods of analysis provided similar results. However, we were unable to adjust for certain variables that were not available in our data sources, i.e. race, body mass index, non-prescription medication use, in hospital medication use, and medication compliance.[17]

(2) Accuracy of codes: One of the concerns using health administrative databases is the accuracy of codes for patient related health information, e.g. chronic kidney disease (CKD) is considered to be the most important risk factor for postoperative AKI and the validity of database codes for CKD is limited (sensitivity: 28.3%; specificity: 94.6%; positive predictive value: 51.9%;

negative predictive value: 86.5%; compared with the reference standard of estimated GFR < 60 mL/min/1.73m^2).[83] However, we used validated database codes whenever possible.[17;77-85]

(3) A key information gap in our study was that we did not have complete information on perioperative ACEi or ARB use. We cannot determine whether patients took their ACEi or ARB around the time of surgery. We did not know: (a) whether it was held prior to surgery and if so which day prior to surgery it was held; (b) if it wasn't held whether the full dose was used just prior to surgery, and (c) if ACEi or ARB was held prior to surgery, if and when it was restarted after surgery during the hospital stay. These are critical issues to guide the safe and optimal use of these medications in the perioperative period.[40-42;51-53]

6.5 Future Directions

Future research studies will better clarify the relationship between preoperative ACEi or ARB use and postoperative AKI.

(1) Prospective cohort studies: Well conducted large multi-centre prospective cohort studies may provide better information on this association.[65] In this regard we have been funded by the Canadian Institutes of Health Research to study the association between preoperative ACEi or ARB use and AKI in an international prospective cohort study, VISION (Vascular Events In Noncardiac Surgery Patients Cohort Evaluation Study; Principal investigator: Dr. PJ Devereaux, McMaster University). In this study AKI will be defined by a ≥ 100% increase in serum creatinine defined according to RIFLE

classification.[1] VISION includes patients' aged 45 years or more undergoing major noncardiac surgery requiring hospitalization. The data collection includes detailed information on demographic characteristics, comorbidities, preoperative and postoperative serum creatinine measurement, postoperative AKI-D, preoperative medications use and whether these medications are temporarily withheld prior to surgery or not. Further, chronic kidney disease is classified according to estimated glomerular filtration rate categories based on modified diet and renal disease (MDRD) equation.[62] This will provide better information on a key comorbid condition as opposed to our current study where the presence of chronic kidney disease was determined with poorly validated database codes.[83] Moreover, we will be able to explore the impact of holding vs. not holding ACEi or ARB prior to surgery. We expect to study a sample of over 30,000 patients recruited across multiple countries after applying our selection criteria.

(2) Future randomized controlled trials: Large randomized controlled trials are required to establish the causal association between preoperative ACEi or ARB use and postoperative outcomes.[22;24;65] If one were to consider a primary outcome of 90-day all-cause mortality, the sample size would be 15,100 patients (Assumptions: i) incidence of 90-day all-cause mortality in 4.5% of patients undergoing major surgery, ii) 1:1 allocation for ACEi or ARB users and non-users, iii) relative risk difference: 20%, iv) no loss to follow-up, v) two tailed, $\alpha = 0.05$, and vi) $1 - \beta = 0.8$)). The sample size could be smaller if it proves reasonable to study the outcome of AKI defined according to changes

in serum creatinine.[1;5] Given the signal of benefit was strongest in the subgroup of patients with chronic kidney disease, enrolling a large number patients with chronic kidney disease may be prudent.

6.6 Study Implications

AKI-D is a serious complication of major surgery. Our study results suggest that preoperative ACEi or ARB use in older people may protect against the complication of AKI-D and may also reduce the risk of postoperative mortality. However, we observed the benefits of preoperative ACEi or ARB use in reducing the risk of AKI-D only in chronic kidney disease patients. Moreover, we cannot rule out the possibility of residual confounding and we did not have key information regarding the nature of ACEi or ARB use in the perioperative period. Large randomized controlled trials are required to address this issue.

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APPENDICES

Appendix A: Data creation plan submitted to ICES

Name and number of study	Acute dialysis following non-urgent surgery: incidence, trends, risk factors, and outcomes: Preoperative ACEi or ARB use 2009 0809 010 000
PIA approved?	Yes, 2009 0809 010 000 (E-mail from Conrad Pow Feb 11th, 2009)
Data creation plan (DCP) update history (AG: Amit Garg; AJ: Arsh Jain; MS: Mitesh Shah; SS: Salimah Shariff; JL: Jin Luo)	Version 24: February 24, 2012 (MS; after a conference call with JL) Version 23: February 21, 2012 (MS; after an email from JL) Version 22: February 14, 2012 (MS, AG, and AJ) Version 21: February 06, 2012 (MS; after a conference call with JL) Version 20: January 25, 2012 (MS, AG, and AJ) Version 19: November 22, 2011 (MS, AG, and SS) Version 18: November 15, 2011 (MS; after discussion with AG) Version 17: November 04, 2011 (MS; after discussion with SS) Version 16: November 03, 2011 (MS; after discussion with SS) Version 15: October 18, 2011 (MS; after discussion with SS) Version 14: September 20, 2011 (MS, AG, and AJ) Version 13: September 11, 2011 (MS; after discussion with SS) Version 12: August 24, 2011 (MS; after discussion with AG) Version 11: July 21, 2011 (MS; after discussion with AG) Version 10: July 07, 2011 (MS; after discussion with AG and AJ) Version 9: July 06, 2011 (MS; after discussion with AG) Version 8: June 20, 2011 (MS; after discussion with AG) Version 7: June 09, 2011 (MS; after discussion with AG) Version 6: February 02, 2011 (MS; after discussion with AG) Version 5: December 20, 2010 (MS) Version 4: November 23, 2010 (MS; after discussion with AG) Version 3: September 28, 2010 (MS) Version 2: September 21, 2010 (MS; after discussion with AG) Version 1: August-September 2010 (MS; after discussion with AG)
Short description of research questions	Research project objective: To determine whether preoperative ACEi (angiotensin converting enzyme inhibitor) or ARB (angiotensin receptor blocker) use is associated with an increased risk of AKI-D following major non-urgent surgery. Hypothesis: Preoperative ACEi or ARB use increases the risk of AKI-D compared to non-use. Design: *Retrospective cohort study* with the following population of interest:

	Individuals age ≥ 66 years without a history of receipt of dialysis or kidney transplantation in the previous 3 years, admitted to a hospital for a non-urgent, elective surgical procedure. We will group these individuals into ACEi or ARB users (exposure group) and non-users (control group) and follow them in the perioperative period. The incidence of AKI-D in ACEi or ARB users and non-users will be determined. Primary outcome: AKI-D (1 to 14 days after surgery) Secondary outcome: Death (1 to 90 days after surgery)

List of datasets:

ODB (available from April 1990; required from September 1994 to November 2010)
Population
☒ Age 66+

RPDB (required from January 1992 to March 2011)

CIHI-DAD (available from April 1988; required from January 1992 to March 2011)
Source
☒ Inpatient
☒ Same day surgery
Institution types
☒ Acute care (insttype = 'AP' or 'AT')
Include suspected/questionable diagnoses?
☒ No

OHIP (available from July 1991; required from January 1992 to March 2011)
Claim Type
☒ All
Code Types
☒ Fee codes
☒ Diagnosis codes

Defining the cohort	
Index date	Date of elective, non-urgent surgical procedure during a hospital admission. If no procedure date is attributed to CIHI-DAD procedural code, use the date for hospital admission as 'index date' *(The date of surgery may be less accurate prior to 1999 as some dates were missing).*

	Begin with the index date between accrual start date and end date (January 1, 1995 to November 30, 2010)
Surgical groups	Only include hospital admissions with evidence of a surgery in one of the following five categories: Cardiac surgery (Category C), Thoracic surgery (Category T), Vascular surgery (Category V), Abdominal surgery (Category A), Retro-peritoneal surgery (bladder, ureter, kidney) (Category R) <u>Study period</u> ☒ Prior to 2002 fiscal year → Include ICD-9/CCP codes ☒ From 2002 fiscal year and onwards → Include ICD-10/CCI codes *We are not studying the following surgical categories: anorectal, breast, external head and neck, lower urological and gynecological, musculoskeletal, neurosurgical, ophthalmologic, skin and soft tissue, unclassified.*
Exclusions	• Exclude hospital admissions for patients undergoing emergent/urgent surgery, also exclude invalid and newborns Coded as "urgent": code = admcat "U" Coded as "emergent": code = admcat "E" Coded as "newborn": code = admcat "N" Coded as "invalid": code = admcat "Z" *These codes are attached to the hospital admission (and not to a given procedure). As such, they will exclude all surgeries done during the course of a non-surgical hospital admission (i.e. patient admitted to a hospital for reasons other than surgery and surgeries performed in this setting are likely to be urgent / emergent). We expect that there will be few such surgeries.* • For the years 2006 to 2008 (January 1, 2006 to December 31, 2008): Exclude all admissions at hospital number 1444 (St. Michael's hospital). *In internal analysis, we observed that there was a far higher than expected percentage of surgical patients requiring post-operative dialysis at St. Michael's hospital between 2006 and 2008. We feel that this may be due to erroneous use of the dialysis codes for cardiopulmonary bypass and have thus chosen to exclude all hospital admissions at St. Michael's hospital during this time-period. Absolute numbers were similarly high and falsely elevated the overall rate of acute dialysis in Ontario.*

Unless otherwise stated, the following applies:
Diagnosis type (dxtype)
☒ All (alldx)

Include suspected/questionable diagnoses?
☒ No

Include abandoned procedures?
☒ No

Exclusions:

- Exclude hospital admissions with invalid or missing IKN (ICES key number), age, or sex

- Exclude those deaths prior to the 'index date' (this does not include the index date)

  Reference date
  ☒ Do not include index date in look-back period (stop at index-1)

- Exclude hospital admissions where a patient's age < 66 years at the time of 'index date' (this includes the index date)

- Exclude hospital admissions associated with non-Ontario residents

- Exclude those patients who do not meet the following criteria: evidence of at least one ODB prescription ≤ 120 days prior to 'index date'(this does not include the index date)

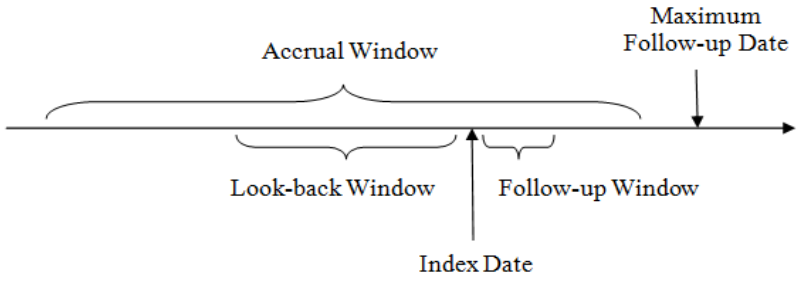
  Reference date
  ☒ Do not include index date in look-back period (stop at index-1)

- Exclude hospital admissions for patients with evidence of dialysis or kidney transplantation in a 3 year look-back period prior to the 'index date' [this does not include the index date]

  Study period
  ☒ Prior to 2002 fiscal year → Include ICD-9/CCP/OHIP fee codes

	☒ From 2002 fiscal year and onwards → Include ICD-10/CCI/OHIP fee codes <u>Reference date</u> ☒ Do not include index date in look-back period (stop at index-1) • Exclude those patients who are on any of the following antihypertensive medications 120 days prior to index date [this does not include the index date]: a) Alpha adrenergic blocker b) Adrenergic neurone blocker c) Centrally acting anti-adrenergic drug d) Vasodilator anti-hypertensive drug e) Direct renin inhibitor f) Potassium sparing diuretic g) Alpha 2-agonist <u>Reference date</u> ☒ Do not include index date in look-back period (stop at index-1) • For patients with multiple eligible surgical procedures within study period (after applying previous exclusion criteria), select one surgical procedure at random. Exclude remaining surgical procedures.

Exposure and control group	
ACEi or ARB users (exposure group)	≥ 1 ODB prescription for ACEi or ARB ≤ 120 days prior to the index date (this does not include the index date). <u>Reference date</u> ☒ Do not include index date in look-back period (stop at index-1)
Non-users (control group)	No evidence of an ODB prescription for ACEi or ARB ≤ 120 days prior to the index date (this does not include the index date). <u>Reference date</u> ☒ Do not include index date in look-back period (stop at index-1)

Time Frame Definitions	
	
Accrual start and end dates	January 1, 1995 to November 30, 2010
Maximum follow-up date	90 days after index date (February 28, 2011) Reference date ☒ Do not include index date in look-forward period (start at index+1)
When does observation window terminate?	Whichever comes first: a) death; or b) 90 days after index date Reference date ☒ Do not include index date in look-forward period (start at index+1)
Look-back window(s) from index date	3 years for comorbid conditions 120 days for ODB medications Reference date ☒ Do not include index date in look-back period (stop at index-1)

Baseline characteristics for ACEi or ARB users and non-users

Report standardized difference in baseline characteristics between ACEi or ARB users and non-users

Diagnosis type (dxtype)

☒ All (alldx)

Study period

☒ Prior to 2002 fiscal year → Include ICD-9/CCP/OHIP fee codes

☒ From 2002 fiscal year and onwards → Include ICD-10/CCI/OHIP fee codes

Include suspected/questionable diagnoses?

☒ No

Demographics

1. Age at index date (years): median (interquartile range)
2. Age group categories (66 to 70, 71 to 75, 76 to 80, 81 to 85, 86 to 90, > 90): total number (percentage)
3. Female: total number (percentage)

Comorbidities (report total number (percentage))

4. Chronic obstructive pulmonary disease (COPD)
5. Cerebrovascular disease
6. Peripheral vascular disease (PVD)
7. Coronary artery disease (CAD) including angina
8. Congestive heart failure (CHF)
9. Chronic kidney disease (CKD)
10. Chronic liver disease

Medication Use (below mentioned medications from 11 to 17; report total number (percentage))
Users: Evidence of at least one ODB prescription in the 120 days prior to index date;
Non-users: No ODB prescription in the past 120 days prior to index date

Reference date
☒ Do not include index date in look-back period (stop at index-1)

11. Oral hypoglycemic (any drug from the following drugs): Sulfonylurea, meglitinide, biguanide, thiazolidinedione, alpha-glucosidase inhibitor
12. Insulin
13. Antidiabetic medications (oral hypoglycemic & insulin)
14. Beta-blocker
15. Calcium channel blocker (CCB)
16. Non-potassium sparing diuretic
17. Statin

Surgical Characteristics (report total number (percentage))

Type of Surgery:

1. Cardiac surgery (Category C)
2. Thoracic surgery (Category T)
3. Vascular surgery (Category V)
4. Abdominal surgery (Category A)
5. Retro-peritoneal surgery (bladder, ureter, kidney) (Category R)

Era of surgery: 1995 to 1998, 1999 to 2001, 2002 to 2004, 2005 to 2007, and 2008 to 2010) (If no procedure date is attributed to CIHI-DAD procedural code, use the hospital admission date as ‘index date’ to determine year of cohort entry)

Outcomes (events) for incidence analysis

Report the following outcomes:

1. "Acute Dialysis (AKI-D)" within 14 days of index surgery (Primary outcome): Evidence of ≥ 1 OHIP code for acute dialysis within 1 to 14 days after index date (acute dialysis outcome must appear during any hospital stay).
   Reference date
   ☒ Do not include index date in look-forward period (start at index + 1)

2. Death within 1 to 90 days after index surgery (Secondary outcome)
   Reference date
   ☒ Do not include index date in look-forward period (start at index + 1)

Statistical Analysis

Association between ACEi or ARB use (exposure) and study outcomes:

- Use logistic regression model
- Exposure group: ACEi or ARB users; Referent group: non-users
- Analysis will be done for (1) Primary outcome; and (2) Secondary outcome
- Report number of events, unadjusted odds ratio (95% confidence interval (CI)) and adjusted odds ratio (95% CI)

Adjust for the following characteristics:

1. Age (in years)
2. Sex (male/female; referent=female)
3. Chronic obstructive pulmonary disease (yes/no; referent=no)
4. Cerebrovascular disease (yes/no; referent=no)
5. Peripheral vascular disease (yes/no; referent=no)
6. Coronary artery disease including angina (yes/no; referent=no)
7. Congestive heart failure (yes/no; referent=no)
8. Chronic kidney disease (yes/no; referent=no)
9. Chronic liver disease (yes/no; referent=no)
10. Antidiabetic medications use (yes/no; referent=no)
11. Beta-blocker use (yes/no; referent=no)
12. Calcium channel blocker use (yes/no; referent=no)
13. Non-potassium sparing diuretic use (yes/no; referent=no)
14. Statin use (yes/no; referent=no)
15. Type of surgery (Categories: C, T, V, A, R; referent surgical category=A)
16. Era of surgery (1995 to 1998, 1999 to 2001, 2002 to 2004, 2005 to 2007, 2008 to 2010; referent=1995 to 1998)

Propensity score matching: Baseline characteristics for ACEi or ARB users and non-users (Report standardized difference in baseline characteristics between both these groups)

Hard match (1:1) on the following characteristics:

1. Age (± 5 years)
2. Sex (male/female)
3. Chronic kidney disease (yes/no)

Perform propensity score matching on all the 16 predefined characteristics included in the primary analysis using a caliper of ± 0.2 standard deviation of all the propensity scores that we derived from all the 16 predefined characteristics. Each non-user could only be selected once to derive the propensity score.

Analysis based on propensity score matching: Association between ACEi or ARB use and outcomes.

- Use logistic regression model
- Analysis will be done for (1) Primary outcome; and (2) Secondary outcome
- Report number of events and odds ratio (95% CI)

Subgroup Analysis:
Effect modification by (1) Chronic kidney disease (yes/no); (2) Era of surgery (1995 to 1998, 1999 to 2001, 2002 to 2004, 2005 to 2007, 2008 to 2010); and (3) Type of surgery (cardiac, thoracic, vascular, abdominal, retro-peritoneal)

- Perform for primary and secondary outcomes
- Use logistic regression model to perform subgroup analyses
- Adjust for all the predefined characteristics included in the primary analysis except the subgroup factor being tested
- Report total number of events and event rate per 10,000 persons followed by unadjusted odds ratio (95% CI) and adjusted odds ratio (95% CI)

Report p-value for the test of effect modification for all the three characteristics mentioned above

Time to event analysis: Perform only for the primary outcome of acute dialysis (AKI-D), censored for (1) death; and (2) end of 14^{th} day after index date

Reference date
☒ Do not include index date in look-forward period (start at index + 1)

- Use a Cox proportional hazards model
- Report number of events, unadjusted hazard ratio (95% CI), and adjusted hazard ratio (95% CI)
- Adjust for all 16 predefined characteristics included in the primary analysis

Appendix B: STROBE[66] checklist

	Item No	Recommendation	Reported on Page no., Appendix, Figure, or Table
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	ii, iii
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	iii
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	1-4, 18, 19
Objectives	3	State specific objectives, including any pre-specified hypotheses	19, 20
Methods			
Study design	4	Present key elements of study design early in the paper	21, Appendix A
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	21-25, Appendix A
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	23, 24, Appendix A
		(b) For matched studies, give matching criteria and number of exposed and unexposed	27, 28, Appendix A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	25-26, 28, 29 Appendix A
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	21, 22, Appendix A,C,D,E
Bias	9	Describe any efforts to address potential sources of bias	25-28, Appendix A
Study size	10	Explain how the study size was arrived at	n/a
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	25, 26, Appendix A
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	26-29, Appendix A
		(b) Describe any methods used to examine subgroups and interactions	28, 29, Appendix A
		(c) Explain how missing data were addressed	n/a
		(d) If applicable, explain how loss to follow-up was addressed	n/a
		(e) Describe any sensitivity analyses	n/a

Results			
Participants	13	(a) Report numbers of individuals at each stage of study—e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Figure 3
		(b) Give reasons for non-participation at each stage	23, 24, Figure 3
		(c) Consider use of a flow diagram	Figure 3
Descriptive data	14	(a) Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders	Table 7
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) Summarise follow-up time (e.g., average and total amount)	30, 31
Outcome data	15	Report numbers of outcome events or summary measures over time	30, Table 8
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 8
		(b) Report category boundaries when continuous variables were categorized	Table 7
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Table 9
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	31, 32, Table 10, Table 11
Discussion			
Key results	18	Summarise key results with reference to study objectives	40
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	44-46
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	40-43
Generalisability	21	Discuss the generalisability (external validity) of the study results	43-48
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	v

Appendix C: Codes used to identify comorbidities

Exclusion: Dialysis and kidney transplantation codes			
		Codes	**Validation**
1.	Dialysis	ICD-9: “V45.1”, “V56.0”, “V56.8”	V45.1, V56.0, V56.8: Sensitivity[85] = 90.4%; Specificity[85] = 93.8%; PPV[85] = 94.0%; NPV[85] = 90.0%
		ICD10: "T824", "Y602", "Y612", "Y622", "Y841", "Z49", "Z992", "N180", "E1022", "E1023", "E1122", "E1123", "E1322", "E1323", "E1422", "E1423"	
		CCP: “51.27”, “51.42”, “51.43”, “51.95”, “66.98”	
		CCI: "1OT53DATS", "1OT53HATS", "1OT53LATS", "1PZ21", "1SY55LAFT", "7SC59QD", "1KY76"	
		OHIP FEE: "R850", "G324", "G336", "G327", "G862", "G865", "G099", "R825", "R826", "R827", "R833", "R840", "R841", "R843", "R848", "R851", "Z450", "Z451", "Z452", "G864", "R852", "R853", "R854", "R885", "G333", "H540", "H740"	
2.	Kidney Transplantation	ICD-9: “V42”	
		ICD-10: “N165”, “Z940”, “T86100”, “T86101”, “T86102”	
		CCP: “67.43”, “67.5”	
		CCI: “1PC85LAXXJ”, "1PC85LAXXK"	
		OHIP FEE: “E762”, “S435”, “E769”, “S434”, “E771”, “Z631”, “G347”, “G348”, “G412”, “G408”, “G409”	

Comorbidities			
		Codes	**Validation**
1.	Chronic kidney disease (CKD)	ICD-9: “403.0”, “403.1”, “403.9”, “404.0”, “404.1”, “404.9”, “582”, “583”, “580”, “581”, “584”, “585”, “586”,	583 to 586 (ICD-9) and N00, N04, N08, N18, N19 (ICD-10): Sensitivity[83] = 28.3%;

		"587", "588.0", "588.8", "588.9", "593.7"	Specificity[83] = 94.6%; PPV[83] = 51.9%; NPV[83] = 86.5%; (Case definition for CKD: 1 claim or 1 hospitalization in past 3 years; compared with the reference standard of eGFR < 60 mL/min/1.73m^2)
		ICD-10: "I12", "I13", "N01", "N03", "N05", "N07", "N14", "N15", "N00", "N04", "N08", "N18", "N19", "N26", "N25", "N137", "N280", "N2888", "N06", "N391"	
		OHIP DX: "403", "580", "581", "585"	
2.	Chronic obstructive pulmonary disease	ICD-9: "491", "492", "496"	Sensitivity[78] = 85.0%; Specificity[78] = 78.4% (Validated for patients > 35 years)
		ICD-10: "J41", "J42", "J43", "J44"	
3.	Cerebrovascular disease	ICD-9: "430", "432.1", "433", "435", "436", "437", "438", "362.3"	436: PPV[82] = 78%
		ICD-10: "I60", "I61", "I63", "I64", "I65", "I66", "I67", "I68", "I69", "G45", "G46", "H34"	I60, I61, I63 to I69, G45,G46: Sensitivity[79] = 89%; PPV[79] = 93%
		CCP: "50.11", "50.12", "51.28"	
		CCI: "1JE50", "1JE57", "1JE87", "1JW50", "1JX57", "1JW57", "1JW76"	
		OHIP FEE: "R792", "N220", "N223", "J050", "N104", "N157", "N120"	
		OHIP DX: "432", "435", "436", "437"	
4.	Peripheral vascular disease	ICD-9: "440.0", "440.2", "440.8", "440.9", "557.1", "443.9", "444"	
		ICD-10: "I700", "I702", "I708", "I709", "I731", "I738", "I739", "K551"	I739: Sensitivity[79] = 74%; PPV[79] = 62%; I700, I702, I708, I709, I731, I738: PPV[84] = 100%
		CCP: "51.25", "51.29", "50.14", "50.16", "50.18", "50.28", "50.38"	

		CCI: "1KG76MI", "1KA76", "1KA50", "1KE76", "1KG26", "1KG50", "1KG57", "1KG87"	
		OHIP FEE: "R787", "R780", "R797", "R804", "R809", "R875", "R815", "R936", "R783", "R784", "R785", "E626", "R814", "R786", "R937", "R860", "R861", "R855", "R856", "R933", "R934", "R791", "R794", "E672", "R813", "R867", "E649"	
5.	Coronary artery disease	ICD-9: "412", "414", "429.2", "429.5", "429.6", "429.7"	
		ICD-10: "I20", "I21", "I22", "I23", "I24", "I25", "Z955", "Z958", "Z959", "R931", "T822"	I21, I22, I25: Sensitivity[79] = 86%, PPV[79] = 96%; I20: Sensitivity[80] = 82%; PPV[80] = 52%; I23: PPV[84] = 98%
		CCP: "48.01", "48.02", "48.03", "48.04", "48.05", "48.1", "48.2", "48.3"	
		CCI: "1IJ26", "1IJ27", "1IJ50", "1IJ54", "1IJ57", "1IJ76"	
		OHIP FEE: "R741", "R742", "R743", "G298", "E646", "E651", "E652", "E654", "E655", "G262", "Z434", "Z448"	
		OHIP DX: "410", "412", "413"	410: Sensitivity[77] = 88.8%; Specificity[77] = 92.8%; PPV[77] = 88.5% 413: Sensitivity[77] = 57.9%; Specificity[77] = 93.9%; PPV[77] = 78.1%
6.	Congestive heart failure	ICD-9: "425", "518.4", "514"	
		ICD-10: "I255", "I500", "I501", "I509", "J81"	I500, I501: Sensitivity[79] = 86%; PPV[79] = 86%;

		CCP: "49.61", "49.62"	
		CCI: "1HP53"	
		OHIP FEE: "R701", "R702"	
		OHIP DX: "428"	428: Sensitivity[77] = 58.5%; Specificity[77] = 96.8%; PPV[77] = 65.1%
7.	Chronic liver disease	ICD-9: "571.0", "571.1", "571.2", "571.3", "571.5", "571.6", "070.2", "070.3", "070.4", "070.5", "V02.6"	PPV[81] = 43 to 93%; NPV[81] = 77 to 100%;
		ICD-10: "K73", "K702", "K703", "K717", "K740","K742", "K743", "K744", "K745", "K746", "K721", "K729", "K766", "K767"	K73, K702, K703, K717, K740, K742, K743, K744, K745, K746: Sensitivity[79] = 58%; PPV[79] = 69%; K721, K729, K766, K767: Sensitivity[79] = 86%; PPV[79] = 63%;

ICD-9: International classification of disease 9th version; ICD-10: International classification of disease 10th version; CCI: The Canadian Classification of Health Interventions; CCP: The Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures; OHIP FEE – Ontario health insurance plan fee codes; OHIP DX: Ontario health insurance plan diagnostic codes;

Appendix D: OHIP fee codes for acute dialysis (AKI-D)

R849	Dialysis - haemodialysis - initial & acute
G323	Dialysis - haemodialysis - acute, repeat (first 3 services)
G866	Intermittent haemodialysis treatment centre
G330	Peritoneal dialysis - acute (up to 48 hours)
G331	Peritoneal dialysis - repeat acute (up to 48 hours) (first 3 services)
G093	Haemodiafiltration - continuous - initial & acute (first 3 services)
G095	Slow continuous ultrafiltration - initial & acute (first 3 services)
G294	Arteriovenous slow continuous ultrafiltration - initial and acute (first 3 services)
G295	Continuous arteriovenous haemofiltration - initial and acute (first 3 services)

OHIP fee codes – Ontario health insurance plan fee codes

Appendix E: Sample of codes used to determine surgical procedures

SURGERY CLASS	DATABASE	SAMPLE OF CODES USED
Cardiac	CIHI-procedure	CCI: 1IJ76 (Bypass, coronary arteries), 1HU80 (Repair, mitral valve)
	CIHI-procedure	CCP: 47.22 (Replacement of mitral valve with tissue graft), 48.09 (Other removal of coronary artery obstruction)
Thoracic	CIHI-procedure	CCI: 1GV87 (Excision partial, pleura), 1GR91 (Excision radical, lobe of lung),
	CIHI-procedure	CCP: 54.0 (Esophagotomy), 44.5 (Complete pneumonectomy)
Vascular	CIHI-procedure	CCI: 1KE76 (Bypass, abdominal arteries), 1JK57 (Extraction, subclavian artery)
	CIHI-procedure	CCP: 50.14 (Endarterectomy of aorta), 50.34 (Resection of aorta with replacement)
Abdominal	CIHI-procedure	CCI: 1NM80LA (Repair, large intestine open approach using apposition technique), 1NF87RK (Excision partial, stomach with vagotomy open approach gastrojejunal anastomosis)
	CIHI-procedure	CCP: 53.51 (Excision of accessory spleen), 57.55 (Left hemicolectomy)
Retro-peritoneal	CIHI-procedure	CCI: 1PG80 (Repair, ureter), 1PB87 (Excision, partial, adrenal gland)
	CIHI-procedure	CCP: 69.4 (Partial cystectomy), 20.2 (Bilateral adrenalectomy)

CCI: The Canadian Classification of Health Interventions; CCP: The Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures; CIHI-DAD: Canadian Institute for Health Information Discharge Abstract Database;
Juurlink *et al*.[80] performed a CIHI-DAD validation study and observed a high sensitivity 0.95 (interquartile range (IQR): 0.89 to 0.99), and positive predictive value 0.91 (IQR: 0.82 to 0.97) to identify surgical procedures using CCI codes. The CIHI-DAD considers CCP prior to 2002 and CCI thereafter to identify surgical procedures.

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