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Acute Kidney Injury and Renal and Cardiovascular Outcomes after Coronary Angiography in Alberta, Canada

by

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Abstract

Acute kidney injury (AKI) following radiocontrast exposure is common in hospitalized adults. AKI may lead to poor outcomes following coronary angiography, and fear of precipitating this complication may be one reason why not all eligible patients receive such invasive procedures. This thesis was undertaken with the overall objective of improving knowledge of the long-term outcomes associated with AKI after coronary angiography. We conducted a systematic review to summarize associations between AKI and adverse outcomes following coronary angiography. Twenty seven of 28 studies reported an increased risk of death in those with AKI and this association persisted in studies that adjusted for confounders and when methods to account for publication bias were applied. AKI was also consistently associated with cardiovascular events; however, studies examining the risks of chronic kidney disease, and end-stage renal disease were limited. To address knowledge gaps, we performed a cohort study examining long-term kidney function and clinical outcomes after coronary angiography in Alberta. Compared to patients without AKI, the adjusted odds of a decline in kidney function 3 months after angiography increased more than 4-fold with mild AKI, and more than 17-fold with moderate or severe AKI. Furthermore, among those with renal impairment after angiography, the adjusted decline in kidney function during subsequent follow-up was greater in those with AKI. AKI was also independently associated with increased long-term risks of death, end-stage renal disease, hospitalization for heart failure, and hospitalization with renal failure. We also compared the risks of AKI in a cohort of patients matched on propensity to receive early invasive versus conservative management for acute coronary syndrome. Early invasive management was associated with a modest

increase in risk of AKI (8.8% versus 5.6%, risk ratio 1.52, 95% CI 1.29 to 1.80); however, the risks of dialysis and end-stage renal disease did not differ between matched groups. These findings suggest that patients who develop AKI after coronary angiography should be targeted for interventions to improve long-term outcomes; however, the risk of AKI should not delay or preclude invasive procedures.

Preface

The following manuscripts based on work from this thesis have been published or are in press. For both papers MJ obtained the data, undertook the analysis, interpreted the results, and wrote the paper, with guidance from his thesis committee (BRH, MT, WAG, MLK, PDF). All authors contributed important intellectual content and provided critical review of the papers. Written permission for reproduction of the articles in their entirety has been obtained from the publisher.

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List of Symbols, Abbreviations and Nomenclature

Symbol	Definition
ACS	Acute Coronary Syndrome
AKDN	Albert Kidney Disease Network
AKI	Acute Kidney Injury
AKIN	Acute Kidney Injury Network
APPROACH	Alberta Provincial Program for Outcomes Assessment in Coronary Heart Disease
CABG	Coronary Artery Bypass Grafting
CI	Confidence Interval
CKD	Chronic Kidney Disease
eGFR	Estimated Glomerular Filtration Rate
ESRD	End-Stage Renal Disease
HR	Hazard Ratio
ICD	International Classification of Diseases
LV	Left Ventricle
MDRD	Modification of Diet in Renal Disease
MOOSE	Meta-analysis Of Observational Studies in Epidemiology
OR	Odds Ratio
PCI	Percutaneous Coronary Intervention
RIFLE	Risk, Injury, Failure, Loss, End-Stage Renal Disease
RR	Risk Ratio
Scr	Serum creatinine

Epigraph

"I have noticed even people who claim everything is predestined, and that we can do nothing to change it, look before they cross the road."

Stephen Hawking

Chapter One: Introduction

1.1 Cardiovascular Disease and Coronary Angiography

Cardiovascular disease is a leading cause of death in Canada[1]. Approximately 1.29 million Canadians were estimated to have cardiovascular disease in 2005, with an increase in prevalence of 19% for men and 2% for women compared to 1994[1]. In contrast to this increase in disease prevalence, rates of death due to cardiovascular disease have in turn declined in Canada over this time[2;3]. This trend may in part be attributable to advances in the management of cardiovascular disease.

Coronary angiography is an important procedure that facilitates the diagnosis and treatment of coronary artery disease. This invasive procedure involves the injection of an iodinated radiocontrast agent into the coronary vessels, is used to diagnose obstructive coronary artery disease, allows for percutaneous coronary intervention (PCI) using angioplasty and stenting, and identifies patients appropriate for coronary artery bypass grafting (CABG) surgery[4]. The average population rate of coronary angiography in Canada has increased in recent years[4], with rates in Alberta now exceeding 400 and 200 procedures per 100,000 population over age 20 years for men and women, respectively[5].

Invasive management approaches involving coronary angiography reduce the risks of recurrent angina, re-hospitalization, myocardial infarction, and long-term mortality in high risk patients with acute coronary syndromes[6], and appear to relieve symptoms in patients with stable coronary artery disease[7]. Despite these benefits, coronary angiography is associated with recognized complications, including acute kidney injury (AKI). AKI may lead to adverse events following coronary angiography, and fear of

precipitating this complication may be one reason not all eligible patients receive this invasive procedure[8-10].

1.2 Hospital-acquired Acute Kidney Injury

Acute kidney injury (AKI) is a common complication of acute illness and is estimated to occur in 4-20% of hospitalized patients, and 30-60% of patients with critical illness[11]. AKI is identified by rapid changes in markers of kidney function, urine volume, or manifestations of kidney failure requiring dialysis. Modern criteria for AKI include the Acute Kidney Injury Network (AKIN) criteria and the Risk, Injury, Failure, and End-stage renal disease (RIFLE) criteria (Tables 1 and 2) which are based upon changes in urine output, serum creatinine concentration, estimated glomerular filtration rate (eGFR), and the need for dialysis [12;13]. These definitions for AKI have evolved in response to the recent recognition that even small changes in kidney function are associated with adverse in-hospital outcomes[14-16].

Observational studies have demonstrated consistent and graded associations between AKI and several adverse clinical outcomes including short-term death, prolonged length of hospital stay, and increased costs of hospitalization[14-16]. Survivors of severe AKI may also continue to experience increased long-term mortality[17] and morbidity following hospital discharge including complications such as chronic kidney disease (CKD) and end-stage renal disease (ESRD)[18-20]. Despite these serious consequences, limited prevention or treatment options are available for AKI[11;21], and avoidance of nephrotoxic

agents and supportive care (aimed at balancing volume status and blood solute concentrations) remain the tenants of management.

1.3 Acute Kidney Injury following Radiocontrast Media Exposure

Radiocontrast exposure is the third leading cause of AKI, in hospitalized patients[11;22]. This form of AKI (often termed contrast nephropathy[23]) is believed to result from ischemic and toxic damage induced by iodinated radiocontrast media[23;24]. The hallmark of AKI following radiocontrast exposure is an increase in the serum creatinine concentration, typically occurring within 1 to 3 days after a procedure involving the intravascular administration of radiocontrast media. In the majority of patients the rise in serum creatinine is transient, resolves within 7 days, and is the only clinical manifestation of AKI[25;26]. Only rarely (< 1% of all cases) is AKI severe enough to require dialysis following radiocontrast administration[24;26;27]. Most patients exposed to intravascular radiocontrast agents experience no deterioration in renal function; however, patients with advanced age, diabetes mellitus, CKD, and heart failure are at increased risk for this form of AKI, particularly when intravascular volume depletion or hemodynamic instability are present[28;29]. Although intravenous fluids and anti-oxidant agents appear to protect against such changes in serum creatinine, their impact on clinical outcomes such as survival and need for dialysis remain uncertain[21;24].

1.4 Acute Kidney Injury and Outcomes after Coronary Angiography

Acute kidney injury (AKI) ranges in incidence from 7 to 15% following invasive coronary angiography or primary angioplasty[30;31] and is usually attributed to the nephrotoxic effects of radiocontrast media [21;23;24]. Several observational studies have demonstrated the prognostic importance of AKI after coronary angiography[23;32;33]. In a prospective study of 1,826 patients undergoing coronary angiography in the United States, in-hospital mortality among patients with AKI was 7.1%, and exceeded that of those without AKI (1.1%)[26]. This association was subsequently confirmed in a larger, retrospective analysis of 7,586 patients from another US center which documented an in-hospital mortality of 22% versus 1.4% for those with and without AKI, respectively[34]. Small absolute or relative increases in serum creatinine of as little as 44 μmol/l or 25% within 1 to 3 days after coronary angiography have been shown to be independently associated with in-hospital mortality and prolonged length of hospital stay following coronary angiography[35]. Some studies have also reported associations between AKI and major adverse cardiovascular events (including target vessel re-occlusion and myocardial infarction) during hospitalization[29;36].

Despite these observations, the true long-term clinical consequences of AKI following coronary angiography have remained controversial because of the observations that death following AKI is often complicated by other acute conditions that are unlikely to be mediated by AKI, including cardiogenic shock, sepsis, respiratory failure, and bleeding[33;34]. While it is known that patients who develop AKI are at increased risk of in-hospital mortality following coronary angiography[26;34], it is less clear if episodes of AKI

are associated with adverse ***long-term*** clinical outcomes following coronary angiography. Specifically, there remains uncertainty about the effects of AKI on the long-term risks of death, cardiovascular events, and the development or progression to chronic kidney disease following these procedures.

1.5 Acute Kidney Injury and Progression to Chronic Kidney Disease

CKD is defined by impaired kidney function or kidney damage present for at least 3 months[37]. CKD may progress to ESRD, a clinical state of kidney failure associated with reduced quality of life, high morbidity and mortality, and considerable utilization of health care resources in part related to the requirement for renal-replacement therapy (chronic dialysis or kidney transplantation)[38-40]. CKD is also a major independent risk factor for the development of cardiovascular disease[41-46]. Cardiovascular disease is highly prevalent among patients with CKD well before they start renal replacement therapy[47] and is the leading cause of mortality in patients with CKD[48-50].

Until recently, the relationship between AKI and progression to CKD and ESRD has received limited attention[51;52]. However, changes in CKD prevalence appear to be insufficient to explain more substantial rises in ESRD incidence[53;54], suggesting that additional factors have contributed to the growth of the ESRD population in recent years, including increases in the incidence and survival of patients with AKI[55;56]. Recent studies suggest that severe episodes of AKI are associated with an increased risk of ESRD requiring chronic dialysis. Among patients with critical illness, the incidence of ESRD 5 years after a severe episode of AKI was 10% in one retrospective series[57], and as

high as 28% for subjects who had AKI superimposed on pre-existing CKD in another study[58]. Severe AKI needing dialysis during hospitalization has recently been associated with an increased risk for chronic renal replacement therapy in later life[18;20;59], and an increased incidence of stage 4 or 5 CKD during post-discharge follow-up[60;61]. While this data illustrates that patients with severe AKI are at increased risk for kidney failure, it remains unclear whether smaller acute changes in kidney function, such as those common following coronary angiography, are also associated with long-term changes in kidney function, the development of CKD, or progression to ESRD.

1.6 Long-term Renal Effects of Radiocontrast Associated Acute Kidney Injury

Although clinical data is limited, experimental data from animals supports the hypothesis that AKI after radiocontrast exposure may have long-term consequences. In animal models, ischemic and oxidative renal injuries cause damage to peritubular capillaries that in turn leads to chronic reductions in microvasculature density[62]. These mechanisms perpetuate further renal hypoxic injury and progression of chronic kidney disease, even following initial recovery from ischemic injury[62-64]. Oxidative renal injury has been shown to increase hypoxia-mediated interstitial fibrosis and thereby facilitate progressive renal injury and dysfunction in rat models[63]. These findings suggest that permanent renal damage may accompany what appear clinically to be only transient renal injuries based on changes in serum creatinine concentration following radiocontrast agents.

Nonetheless, there is little clinical data on long-term renal effects of radiocontrast associated AKI. In one case – control study a graded association was observed between

increased exposure to radiocontrast media and higher risk of treated ESRD[65]. Furthermore, in a cohort study of patients hospitalized with myocardial infarction, AKI was associated with increased risk of ESRD during long-term follow-up[66]. The association between mild or transient episodes of AKI following coronary angiography and long-term changes in kidney function are not clear. Further research is needed to determine whether such episodes are associated with other long-term complications of CKD, including progression to ESRD and cardiovascular events.

1.7 Additional Risk Factors for Acute Kidney Injury after Coronary Angiography

Data from observational studies suggest that several non-procedural features are related to the risk of AKI after coronary angiography, including patient age, comorbidities (diabetes mellitus, pre-existing CKD, and heart failure), and hemodynamic impairment (identified by cardiogenic shock or requirement for an intra-aortic balloon pump)[28;29;33]. Furthermore, in a large cohort of patients hospitalized with myocardial infarction in the United States, less than 15% of those who developed AKI underwent an invasive coronary procedure[66]. These findings illustrate that patient related factors, independent of radiocontrast media exposure, play an important role in AKI in these settings[21;33]. Although this has important implications surrounding clinical decisions to perform coronary angiography, the risks attributable to procedural versus patient factors remain unclear as observational studies have not examined rates of AKI and clinical outcomes between comparable groups of patients that differ by exposure to radiocontrast agents[67]. To fill this knowledge gap, studies are needed which compare the risk of AKI and

downstream clinical outcomes between patients who receive invasive management with coronary angiography and those managed non-invasively.

1.8 Outline of Thesis Contents

This thesis examines the relationships between AKI and long-term outcomes after coronary angiography. This body of research draws upon several valuable data sources from the province of Alberta. The Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease (APPROACH) is a prospective data collection initiative that provides detailed clinical and outcome information on all patients undergoing coronary angiography in the province of Alberta since 1995[68]. The Heart Alert Registry is a similar initiative of APPROACH that provides information on patients admitted to 6 Alberta hospitals for acute coronary syndrome since 2003, and allowed us to compare outcomes between different treatment strategies, both with and without invasive coronary angiography. The Alberta Kidney Disease Network (AKDN) repository of laboratory data provided serum creatinine measurements from laboratories across the province of Alberta (population 3.5 million)[69] and allowed us to identify episodes of AKI and their severity according to standard criteria, and also enabled us to examine intermediary events in the form of long-term changes in kidney function. Finally we were able to study additional clinical outcomes by linking to provincial administrative databases (to identify vital status, hospitalization dates, and admitting diagnoses based on *International Classification of Diseases* 9-CM or 10 codes), and Alberta renal program databases (to identify additional outcomes of relevance to the study of kidney disease including dialysis initiation and kidney transplantation).

Each of the chapters of this document reports on a unique thesis component formatted for independent publication as part of a paper based thesis; however, all components are linked by the ***common objective of improving knowledge of the long-term clinical outcomes associated with AKI in the setting of coronary angiography.*** Each chapter represents an independent study distinguished by a specific research question, study cohort, or set of methods. Chapter 2 is comprised of a systematic review of observational (cohort) studies summarizing published data on AKI and adverse clinical outcomes following coronary angiography. This study included a qualitative summary of findings, quantitative results based on meta-analysis, exploration of heterogeneity through meta-regression and subgroup analyses, and examination of the potential influence of publication bias. Chapter 3 analyses the relationship between AKI and long-term changes in kidney function during follow-up after coronary angiography. In this study we applied methods for the analysis of longitudinal data, including mixed effects models, to characterize changes in serum creatinine and estimated glomerular filtration rate during follow-up. Chapter 4 examines the long-term risks of death, cardiovascular events, and renal outcomes associated with AKI after coronary angiography. A Cox proportional hazards model for correlated unordered events of different type, stratified by outcome type, was fit in order to model the risks of these competing events. Chapter 5 compares the risks of AKI, acute dialysis, ESRD, and survival between patients receiving different treatment strategies for acute coronary syndromes, including early invasive, conservative, and medical approaches to management. This study employed propensity score matching in an attempt to reduce treatment by indication bias. Finally, Chapter 6

summarizes and synthesizing the findings of the thesis. This concluding chapter discusses the limitations of the studies, clinical implications, and directions for future research aimed at improving outcomes in those with AKI after coronary angiography.

Table 1.1 – AKI Network criteria for Acute Kidney Injury[12]

Stage	Serum creatinine criteria
1	increase of 50% to 100% from baseline, or increase of more than or equal to 0.3mg/dL (26.4µmol/L)
2	Twofold to threefold increase from baseline
3	Greater than threefold increase from baseline or serum creatinine ≥4 mg/dL (354 µmol/L) with acute rise >0.5 mg/dL (44µmol/L) or requirement for renal replacement therapy

Abbreviations: AKI = Acute Kidney Injury

Table 1.2 - RIFLE criteria for Acute Kidney Injury[13]

Class	Serum creatinine criteria
Risk	increase of 50% from baseline
Injury	Twofold increase in from baseline
Failure	Threefold increase in from baseline or serum creatinine ≥4 mg/dL (26.4 μmol/L) with acute rise >0.5 mg/dL (44 μmol/L) or requirement for renal replacement therapy
Loss	Acute kidney injury with requirement for renal replacement therapy >4 weeks

Chapter Two: Acute Kidney Injury and Adverse Clinical Outcomes Following Coronary Angiography: A Systematic Review and Meta-analysis

2.1 Abstract

Background - Acute kidney injury (AKI) following radiocontrast exposure is the third leading cause of AKI in hospitalized adults. We did this systematic review and meta-analysis to characterize the associations between AKI following coronary angiography and adverse clinical outcomes.

Methods - We identified studies using MEDLINE (1950 to June 2010) and EMBASE (1980 to June 2010), manual bibliographic searches, and contact with experts. We included observational studies that characterized outcomes among patients with and without AKI (based on changes in serum creatinine) following coronary angiography. Eligible studies reported at least one of mortality, cardiovascular events, length of hospital stay, progressive chronic kidney disease or end stage renal disease.

Results - Thirty-three observational studies (122,015 participants) met inclusion criteria. Of 28 studies reporting mortality, 27 reported an increased risk of death in those with AKI, although the effect size varied between studies (I^2=94.6%). Between-study heterogeneity was partially explained by whether adjustment for confounders was performed (21 studies with adjustment; pooled adjusted RR 2.66, 95% CI 2.00-3.55, I^2=95.5%) versus (7 studies without adjustment; pooled crude RR 8.70,95% CI 3.81-19.86, I^2=68.9%) and by duration of follow-up (7 studies; short-term follow-up; pooled adjusted RR 5.60, 95% CI 2.40-13.02, I^2=96.4%) versus (14 studies; follow-up > 6 months; pooled adjusted RR 1.86, 95% CI 1.55-2.24, I^2=85.5%). AKI was consistently associated with an increased risk of cardiovascular events and prolonged hospitalization, although heterogeneity was also present for these outcomes. Two studies reported on the

risk of progression to end stage renal disease (pooled unadjusted RR with AKI 15.26; 95% CI 1.86-125.01, I^2=0.0%).

Conclusions - AKI following coronary angiography is associated with an increased risk of mortality, cardiovascular events, and prolonged hospitalization. Adequately powered randomized trials are needed to evaluate the effects of AKI prevention and treatment strategies on the risk of these clinical outcomes following coronary angiography.

2.2 Background

Acute kidney injury (AKI) commonly follows coronary angiography, and is often attributed to radiocontrast associated kidney injury[24;32] -- the third leading cause of AKI in hospitalized patients[22]. Patients at high risk of cardiovascular disease, including those with diabetes mellitus, chronic kidney disease, and heart failure are at particularly high risk for this form of AKI[23;28;29]. The primary manifestation is an increase in serum creatinine concentration, typically occurring 1 to 3 days after the procedure[24]. This rise in serum creatinine usually resolves within 7 days[25], and AKI following radiocontrast administration rarely requires acute dialysis treatment[24;28].

Observational studies suggest that small changes in kidney function following contrast media exposure may be independently associated with longer hospital admission[70;71], unsuccessful revascularization[29;72], cardiovascular events[73;74], and increased mortality[34;35]. Although some of the prominent findings from published studies have been summarized in narrative reviews[23;32;75], the nature of the relationships between AKI and other relevant patient-centred clinical outcomes, the quality of existing studies, and features that account for heterogeneous results among studies remain unclear.

We did a systematic review and meta-analysis of observational studies that examined the association between AKI following coronary angiography and adverse clinical outcomes, including mortality, cardiovascular events, progression to chronic kidney disease (CKD) or end-stage renal disease (ESRD), and prolongation of hospitalization.

2.3 Methods

We adhered to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines[76] and followed a pre-specified study protocol.

2.3.1 Search Strategy

We systematically searched MEDLINE (1966 to June 2010) and EMBASE (1980 to June 2010) for studies describing the association between AKI (identified based on changes in serum creatinine concentration) and death, cardiovascular events (including cardiovascular mortality, myocardial infarction, target vessel revascularization, or heart failure), progression to CKD, chronic dialysis, or ESRD, and length of hospital stay among patients undergoing coronary angiography. We also searched the reference lists of all identified relevant publications, and contacted experts in coronary angiography and AKI. We limited inclusion to studies published in English.

Three search themes were combined using the Boolean operator "and". The first theme, coronary angiography, combined exploded versions of Medical Subject Headings (MeSH) *angiography, contrast media, angiocardiography, heart catheterization, angioplasty, transluminal, percutaneous coronary angioplasty,* or *myocardial revascularization,* or text words *coronary angiography, cardiac catheterization, percutaneous coronary intervention, PCI, angiography, coronary revascularization,* or *cardiac angiography*. The second theme, combined exploded versions of the MeSH terms *acute kidney failure* or *creatinine* or text words *acute kidney injury, acute kidney failure, acute renal failure, acute renal insufficiency nephropathy, contrast nephropathy,*

or *contrast induced nephropathy*. We used the approach of Egger et al. to identify studies with an observational design[77].

2.3.2 Selection Criteria

Two reviewers independently identified potentially eligible articles by performing an initial screen of titles and abstracts. Articles were further considered for inclusion if they reported data from an original study (review articles were excluded) and reported on clinical outcomes according to AKI status following diagnostic or therapeutic coronary angiography. We used broad inclusion criteria for studies, including varying definitions for acute kidney injury data and information on any clinical outcomes as they were defined by the primary studies. Articles were retained when either of the reviewers believed that it should be retained or when there was uncertainty as to eligibility based on title and abstract alone.

Selected articles were subsequently screened based upon a full text review. To be included, studies had to be observational studies of participants following diagnostic or interventional coronary angiography, with a comparison between those with AKI (based on a relative or absolute change in serum creatinine) and those without AKI. We included any study reporting on one or more of mortality, cardiovascular events (including myocardial infarction, heart failure, cardiac arrhythmia, cerebrovascular accident, need for revascularization, hospitalization for cardiovascular event, death, or composite of these events), progression to CKD, ESRD (including chronic dialysis), or length of hospital stay. When more than one publication was identified from the same

cohort examining the same study outcome, we included data from the article with the largest sample size.

2.3.3 Data Extraction

Two reviewers independently extracted data on baseline patient characteristics, procedural characteristics, criteria used to define AKI, and duration of follow-up. We also collected data on methodological features indicative of study quality, following the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines[76]. These included specification of the inclusion/exclusion criteria, the inclusion of consecutive participants in the cohort, losses to follow-up < 10% or appropriate handling of losses to follow-up, blinding of exposure status for outcome assessment, and statistical adjustment for the major confounders (age, diabetes mellitus, coronary artery disease, heart function/failure, and baseline kidney function). The main exposure variable of interest was acute kidney injury, and the reference group was those without acute kidney injury in each study. Most studies (n=31) identified dichotomous groups (with AKI versus without AKI); however 1 study further categorized severity of AKI based on magnitude of the change in serum creatinine, and 1 study categorized AKI based on whether it persisted for greater than or less than 7 days. In order to pool these results in a consistent manner, we combined results for these additional categories within a single exposure group (with acute kidney injury) in the pooled analysis, and performed meta-regression and subgroup analyses according to the serum creatinine criteria used to define groups with AKI (ie. increase in serum creatinine concentration >25% or 0.5 mg/dL [44 μmol/L] versus > 50% or 1.0 m/dL [88 μmol/l]) in each study.

Study outcomes of interest were mortality, cardiovascular events, progressive CKD, ESRD, and length of hospital stay. The definitions used for non-fatal events varied across studies. We considered major adverse cardiovascular events to include myocardial infarction, heart failure, cardiac arrhythmia, cerebrovascular accident, need for revascularization, hospitalization for cardiovascular event, death, or a composite of these events. We considered the progression of CKD according to the criteria used in each study provided it was based on a change in estimated glomerular filtration rate ≥ 3 months after angiography, and ESRD as the requirement for chronic dialysis following hospital discharge. Length of stay was defined based on the number of days from either hospital admission or angiography to discharge, depending on the study design. The duration of follow-up for clinical outcomes varied across studies. We grouped studies on the basis of short-term (in-hospital or at 30 days) or long-term follow-up (post-discharge or ≥ 1 year) and performed meta-regression and subgroup analysis on the basis of this distinction.

We recorded risk ratios (RR), hazard ratios (HR), or odds ratios (OR) for the dichotomous clinical outcomes of interest (mortality, major adverse cardiovascular events, and ESRD), and the means and standard deviations for continuous measured outcomes (change in estimated glomerular filtration rate, days in hospital) for patients with AKI compared with those without AKI. Adjusted values were obtained wherever reported. We collected crude values if adjusted results were not presented.

2.3.4 Statistical Analysis

We pooled RRs for dichotomous outcomes, and means for continuous outcomes across studies. To transform ORs to RRs we used the formula $RR=OR/[(1-P_0)+(P_0 \times OR)]$, where P_0 is the incidence of the outcome of interest in the unexposed group[78]. We pooled the natural logarithm of the RRs of binary outcomes and determined the weighted mean difference of continuous outcomes using the random effects model of DerSimonian and Laird[79]. We used the Cochrane Q statistic (at a significance level of $p<0.10$), and the I^2 statistics to assess for heterogeneity across studies[80;81]. Subgroup analyses, stratified by study population characteristics and study methodology criteria were also performed. We evaluated funnel plots and used Begg`s test to detect small study effects suggestive of publication bias[82;83]. We used the Duval and Tweedie nonparametric `trim and fill` procedure to determine the possible effect of publication bias on pooled estimates by imputing the estimate of effect of hypothetical `missing`studies, and imputing a pooled estimate that included these studies[84]. All analyses were performed in Stata version 11 (StataCorp, College Station, Texas) using the "metan", "metareg", and "metapub" commands.

2.4 Results

Our search strategy yielded 3,351 unique citations. We excluded 3,283 citations based on screening of title and abstract, leaving 68 articles for full-text review. We subsequently excluded 35 studies that did not meet inclusion criteria, including 10 articles that were based on overlapping cohorts of patients and were excluded to avoid duplicate inclusion

of data (Figure 2.1). There was good agreement between reviewers on the final articles eligible for inclusion (kappa=0.824).

2.4.1 Study Characteristics

Characteristics of the 33 studies included in the systematic review are provided in Table 1[27;29-31;34-36;70-74;85-105]. Studies were published between 1990 and 2010, and 18 were from the United States, 11 from Europe, 2 from Asia, and 2 from Israel. The number of participants ranged from 78 to 27,608 (122,015 participants in total) and the mean age ranged from 56.4 to 75.4 years across studies. Most studies included patients both with and without CKD at baseline (range of proportions with CKD 3.2% to 38.3% according to individual study definitions of CKD), although 4 studies[27;30;89;91] included only patients with impaired baseline kidney function, and 2 studies[96;101] excluded patients with elevated serum creatinine at baseline. Twenty-five studies included only patients receiving percutaneous coronary interventions (including 8 studies of patients receiving primary percutaneous intervention for ST segment elevation myocardial infarction), whereas 4 studies[30;89;99;105] included patients receiving diagnostic coronary angiography.

The definition of AKI was based on a relatively small change in serum creatinine concentration in all studies; 27 studies identified AKI on the basis of an increase in serum creatinine concentration exceeding either 25% and/or 0.5 mg/dL (44 μmol/L), whereas 5 studies[29;70;90;96;103] identified AKI based on a greater than 50% and/or 1.0 mg/dL (88 μmol/L) increase in serum creatinine concentration, and 1 study[35] incorporated both definitions (Table 2.1). The duration of follow-up varied between studies, with 11

studies using follow-up to hospital discharge, 2 studies with follow-up 30 days post-procedure, and 20 studies with long-term follow-up ranging between 6 months and 5 years.

The specific definitions of the outcomes for each study are shown in Table 2.2. Adjusted RRs of mortality were obtained from 21 studies[29;34-36;71-74;85;87-91;93-96;100;104;105], whereas only unadjusted RRs of mortality could be determined from 7 studies[30;86;92;97-99;101-103]. One study did not contribute to the pooled analysis for mortality because no deaths were recorded[92]. Adjusted RRs of major adverse cardiovascular events were determined from 8 studies[29;34;72-74;96;98;101], but only unadjusted RRs were obtained from 2 studies that included this outcome[36;71]. No studies reported the adjusted RR of ESRD, although two studies provided data to determine the unadjusted RR [27;88]. Eight studies reported the unadjusted mean length of hospital stay[31;36;71;72;98;101;104;105], and one study reported an adjusted increase in length of hospital stay equivalent to 1.6 additional days with AKI ($p=0.005$)[70]. No form of adjustment was provided for the study that reported progression of CKD[89]. Adjustment was performed for age in 20 studies, diabetes mellitus in 18 studies, severity of coronary artery disease in 11 studies, heart failure (based on LV function, pulmonary edema, or cardiogenic shock) in 21 studies, and baseline kidney function (serum creatinine or eGFR) in 13 studies (Table 2.2).

The methodological quality and features of study design are provided in Table 2.3. Inclusion and exclusion criteria were clearly specified in all but one study, and all but one study enrolled consecutive patients in the cohort. There were no losses to follow-up in 29

studies, 1 study which did not report on losses to follow-up, and 3 studies reported losses to follow-up ranging from <1 to 17%. None of these studies reported whether losses to follow-up were associated with key characteristics. Study personnel who evaluated outcomes were blinded to exposure status in only two studies.

2.4.2 Association between AKI and Mortality

Results from 28 studies examining mortality, including a total of 120,575 participants, showed evidence of statistical heterogeneity (Q statistic, $p<0.001$; I^2, 94.6%). However, 27 of the 28 studies reported an increased risk of death in those with AKI after coronary angiography (Figure 2.2). Risk ratios from studies that reported unadjusted results were significantly greater than those obtained from studies that provided adjusted estimates (meta-regression, p=0.009). For example, based on 7 studies (with 6,257 participants) that reported unadjusted results, the pooled crude RR of death was 8.70 (95% CI 3.81 – 19.86, Q statistic p=0.04, I^2=68.9%), whereas, the pooled adjusted RR from 21 studies (with 114,318 participants) with adjusted results was 2.66 (95% CI 2.00 – 3.55, Q statistic $p<0.001$, I^2=95.5%). Requiring a more stringent definition of AKI (increase in serum creatinine concentration > 50% or 1.0 mg/dL [88 μmol/L] versus >25% or 0.5 mg/dL [44 μmol/L]) did not appear to influence the risk of mortality associated with AKI (meta-regression, p=0.50).

We performed further meta-regression to explore reasons for heterogeneity across the 21 studies that reported adjusted RRs. Features of the study population including mean age (<65 versus >65 years), proportion of participants with diabetes mellitus (<25 versus

>25%), proportion of patients with CKD prior to angiography (< 25 versus >25%), type of procedure (interventional versus diagnostic procedures), and inclusion of patients without ST segment elevation myocardial infarction (yes versus no) did not explain differences between study results (meta-regression p>0.10 for all comparisons). Studies with short-term follow-up (to hospital discharge or 30 days post-procedure) reported higher adjusted RRs of death associated with AKI than studies with long-term (>6 month) follow-up (meta-regression p=0.04). Seven studies (59,266 participants) had short term follow-up with a pooled adjusted RR of 5.60 (95% CI 2.40 – 13.02, Q statistic p<0.001, I^2=96.4%), while 14 studies (55,052 participants) had long-term follow-up, with a pooled adjusted RR of 1.86 (95% CI 1.55 – 2.24, Q statistic p<0.001, I^2=85.0%). Results from studies that met at least 4 of the methodological criteria for good study quality (15 studies, 78,770 participants, RR 2.00, 95% CI 1.66 – 2.42, Q statistic p<0.001, I^2=87.1%) were more conservative than those from the remaining studies of lower methodological quality (13 studies, 41,805 participants, RR 6.37, 95% CI 3.48 – 11.66, Q statistic p<0.001, I^2=90.2%) (meta-regression p=0.001).

The funnel plot for studies reporting adjusted RRs for mortality was asymmetrical (Figure 2.3A). The possibility of publication bias was further suggested by Begg's test (z=2.25; p=0.027). When the trim and fill procedure was used to impute results for hypothesized unpublished studies[84] (Figure 2.3B), the pooled adjusted RR was attenuated but continued to show a significant association between AKI and mortality (RR 1.76 95% CI 1.28 – 2.42).

2.4.3 Association between AKI and Cardiovascular Events, ESRD, CKD, and Length of Hospitalization

Of 10 studies (53,834 participants) reporting on cardiovascular events, all reported an increased risk associated with AKI after coronary angiography (Figure 2.2). The pooled RR from these studies for cardiovascular events was 2.55 (95% CI 1.50 – 4.33) but there was again evidence of statistical heterogeneity (Q statistic, $p<0.001$; I^2, 97.0%). The reporting of crude versus adjusted RRs did not appear to influence the risk of cardiovascular events associated with AKI (meta-regression p=0.45). Neither study population characteristics nor study quality features further explained heterogeneity. There was no evidence of publication bias among studies evaluating cardiovascular events based on Begg's test (z=, p=0.271) or by the funnel plot.

Two studies (3,675 participants), which provided only unadjusted results, reported on the association of AKI with risk of progression to ESRD (pooled crude RR 15.26; 95% CI 1.86-125.01, Q statistic, $p<0.987$; I^2, 0%) (Figure 2.2). For the one study that reported on progression of CKD, the mean unadjusted decline in eGFR was 14 (95% CI 6 – 22) mL/min/1.73m^2 greater for participants with AKI at 5 years after coronary angiography. All studies examining length of hospital stay reported longer admissions in patients with AKI compared to those without AKI. Eight studies (19,014 participants) reported a mean length of hospital stay which was longer for participants with AKI in all of these studies, although there was heterogeneity in the size of this effect (Q statistic, $p<0.001$, I^2 98.2%), with substantial variability in length of hospitalization between studies (Figure 2.4).

2.5 Discussion

We identified several observational studies examining adverse clinical outcomes associated with AKI following coronary angiography. AKI was consistently associated with mortality across a range of studies with varying population characteristics and this association was also present (although attenuated) in studies of high methodological quality. The association between AKI and mortality remained present for both short and long-term follow-up, and when techniques to account for potential publication bias were applied. These results confirm the association between AKI after coronary angiography and mortality, although whether this represents a causal relationship remains unclear.

The cohort studies in this systematic review illustrated a temporal relationship between AKI and death following coronary angiography. Although we did not detect a dose response relationship in risk of death with more severe episodes of AKI, between study heterogeneity may have obscured such a finding. In one study which categorized AKI severity according to the magnitude of serum creatinine increase after coronary angiography, larger changes were associated with a higher risk of 30 day mortality[35], and such a dose-response relationship with risk of death has also been seen in other studies of AKI outside the setting of coronary angigraphy[16;66;106]. However, the biological mechanism by which AKI may lead to death remains unclear. Severe forms of AKI (that often require dialysis) could predispose to early mortality following coronary angiography due to volume overload, electrolyte disturbances, or uremia; however, it is less clear how relatively small changes in kidney function might increase this risk. It has been hypothesized that patients who develop AKI after radiocontrast exposure are treated

more conservatively so as to preserve remaining kidney function[107;108]. Further research is needed to delineate how patients who develop AKI after coronary angiography are subsequently managed – especially studies focusing on differences in use of revascularization procedures, antiplatelet agents, anticoagulants, beta-blockers, and inhibitors of the renin angiotensin system. Conversely, AKI may be a marker of severity of illness that accompanies hemodynamic instability and ischemia, and may not lie on a causal pathway to mortality. Further research is needed to understand disease mechanisms in AKI, including experimental studies that clarify if AKI prevention leads to improved survival.

The high risk of death following AKI could be mediated by major adverse cardiovascular events. For this reason we identified several studies that examined cardiovascular outcomes following coronary angiography and found that AKI was also associated with an increased risk of these events. Most of these studies examined composite cardiovascular outcomes including cardiovascular mortality, and coronary events such as myocardial infarction, or need for repeat coronary revascularization during follow-up. The risks of coronary vascular disease and cardiovascular events associated with chronic kidney disease are well established[41;50] and are thought to involve mechanisms including atherosclerosis, vascular calcification, and left ventricular hypertrophy[109;110]. Further studies are needed to delineate whether AKI increases the risk of cardiovascular events in addition to that associated with pre-existing comorbidities including markers of CKD (ie. reduced eGFR and albuminuria)[41;43;111].

The effect of AKI on long-term renal outcomes following angiography has been controversial. Most studies have reported resolution of renal impairment within days post-procedure[25], although some observational data has suggested an increased risk of ESRD associated with radiocontrast media exposure[65]. We identified only 3 studies that reported risks of long-term decline in eGFR or progression to ESRD in those with AKI, although none of these reported adjusted results. Severe episodes of AKI have been linked to the development of CKD and ESRD[18;20;60], although whether small changes in kidney function such as those usually associated with radiocontrast exposure independently increase these risks requires further investigation. Persistent kidney dysfunction following an episode of AKI could lead to CKD and its associated long-term complications, though further studies are needed to determine whether this mechanism explains the increased long-term risks for cardiovascular events and death associated with AKI after coronary angiography.

This systematic review has several limitations. First, there was evidence of publication bias among studies that reported on mortality. However, we found that the relation between AKI and risk of death remained after applying techniques to adjust for this form of bias. Second, most studies evaluated composite cardiovascular outcomes, with the risks of specific component events remaining uncertain. Future studies should examine risks for individual cardiovascular outcomes including myocardial infarction, heart failure, and arrhythmia episodes to better understand potential mechanisms for the association between AKI and cardiovascular morbidity and mortality. Third, studies examining associations between AKI and the development of CKD and ESRD did not

address potential confounders. Patients with pre-existing CKD are among those at highest risk for AKI following radio-contrast media exposure, and also at highest risk for progression to the later stages of CKD. Observational studies that capture detailed information on kidney function prior to coronary angiography and with long-term follow-up are needed to examine long-term changes in kidney function, and progression to ESRD. Fourth, we observed substantial unexplained statistical heterogeneity in the magnitude of effect sizes between studies for several outcomes. For differences in the length of hospital stay, this heterogeneity may be explained by differences in clinical practices between institutions, while, for all outcomes, variations in study design (including the definition of AKI and the length of follow-up) appeared to explain some of this variation. Despite the absence of effects due to differences in study populations detected by meta-regression, these clinical differences may still account for heterogeneity, as these tests have low power when performed at the study level[77]. Nonetheless, despite quantitative differences in the magnitude of risk differences, the qualitative findings from our systematic review were very consistent for all the outcomes examined.

In conclusion, this systematic review demonstrates that AKI after coronary angiography is associated with short and long-term mortality, and cardiovascular events. Additional high quality observational studies are needed to characterize the independent risks of progressive loss of kidney function and ESRD associated with AKI following coronary angiography. To date, clinical trials for prevention of AKI in the setting of coronary angiography have focused on small changes in serum creatinine concentration between 2

to 5 days after angiography[112]. Whether preventing this surrogate outcome would lead to improved clinical outcomes remains uncertain. Randomized trials, powered for these clinical end-points, are needed to evaluate the effects of prevention and treatment strategies for AKI following coronary angiography.

Table 2.1 – Characteristics of Studies Included in the Systematic Review

Author, Country, Year	Number Participants	Patient and Procedural Characteristics				AKI Definition	Duration of Follow-Up
		Age (mean), years	Prevalence and Definition of CKD	% PCI	Indication for Angiogram		
Aronow, United States, 2001	359	Median 62	5.6% SCr above upper limit of normal	100.0	8.1% AMI within 24h	increase in SCr to >2.0 mg/dL or a 50% increase above a pre-procedure baseline	hospital discharge
Assali, Israel, 2007	324	63.8	25.3% eGFR <60 ml/min/1.73m²	100.0	100.0% STEMI	>25% or 0.5 mg/dL increase above baseline in SCr after PCI	30 days
Bartholomew, United States, 2004	20,479	64.5	Mean CrCl 78 ml/min	100.0	NR	≥1.0 mg/dL increase in Scr from the baseline level after PCI	hospital discharge
Bouzas-Mosquera, Spain, 2007	315	Median 67	19.4% eGFR <60 ml/min/1.73m²	100.0	100.0% STEMI	increase in the Scr ≥0.5 mg/dL in the 72 h following the procedure compared to Scr concentration at hospital admission	median 1.3 years
Brown, United States, 2008	7,759	65.0	28.1% eGFR <60 mL/min/1.73m²	100.0	NR	>25% increase in Scr from baseline within 48 hours	7.5 years
Chen, China, 2008	936	60.9	29.5% SCr ≥ 1.5 mg/dl	100.0	0.0%	absolute increase in Scr >0.5 mg/dL at 48h after PCI	6 months
Dangas, United States, 2005	7230	64.4	27.4% eGFR <60 mL/min/1.73m²	100.0	35.5% NSTEMI	an increase of ≥25% and/or ≥0.5 mg/dL in pre-procedure Scr at 48 hours after the procedure	1 year
Ergelen,	2529	56.4	NR	100.0	100.0%	increase in Scr of at least 0.5 mg/dL or	hospital

Turkey, 2010					STEMI	at least 25% from baseline within 72h of radiocontrast administration	discharge
From, United States, 2008	3236	64.0	38.3% eGFR <60 mL/min/1.73m²	NR	NR	Scr elevation of 25% or of more than 0.5 mg/dL within 7 days of contrast exposure	mean 16 months
Goldenberg, Israel, 2009	78	56.4% ≥70 years	100% eGFR <60 mL/min/1.73m²	62.8	0.0	increase in Scr of ≥0.5 mg/dL or a >25% increase above baseline within 48h after contrast agent administration	median 4.9 years
Gruberg, United States, 2000	439	70.0	100.0% SCr ≥1.8 mg/dL	100.0	NR	increasein Scr ≥25% within 48h or procedure or requiring dialysis	1 year
Gupta, United States, 2005	9067	64.1	4.1% SCr >1.5 mg/dL	100.0	7.4% AMI	rise in Scr greater than 1 mg/dL from the baseline value	mean 3.2 years
Harjai, United States, 2008	973	64.9	25.4% CrCl <60 mL/min	100.0	NR	(1) a twofold increase in SCr over baseline value with increase>2.0 mg/dL or dialysis, (2) increase in SCr >1.0 mg/dL, (3) increase in SCr >0.5 mg/dL, (4) increase in SCr >25%	6 months
Hölscher, Germany, 2008	412	67.1	100.0% SCr >1.3 mg/dL	NR	0.0%	increase in SCr of 0.5 mg/dL or more within 72h of constrast agent administration	mean 649 days
Jabara, United States, 2009	275	62.0	24.0% eGFR >60 mL/min/1.73m²	100.0	45.0% ACS, 4.0% STEMI	an absolute increase in Scr ≥0.5 mg/dL over baseline, or a relative decrease in eGFR ≥25% from baseline, or a relative increase in Scr ≥25% over baseline 3 to 5 days post procedure	hospital discharge
Kini, United States, 2009	12997	63.7	14.3% SCr ≥1.5 mg/dL	100.0	NR	increment of 25% or more in baseline Scr post-procedure on days 1 through 4 after contrast exposure	1 year

Kowalczyk, Poland, 2007	1486	58.4	19.0% eGFR <60 mL/min/1.73m²	100.0	100.0% AMI	rise in SCr or 0.5 mg/dL or a 25% increase from the baseline value within 48 hours after PCI	mean 29.7 months
Levy, United States, 1996	348	Median 66	Median Baseline SCr 141 µmol/L	NR	14.6% AMI	increase in Scr of at least 25% from baseline, to at least 177 µmol/L (2 mg/dL), within 2 days of radiocontrast administration	hospital discharge
Lindsay, United States, 2003	5967	62.8	Normal baseline SCr	100.0	0.0%	increase in Scr of ≥50% from baseline after PCI	1 year
Marenzi, Italy, 2004	208	62.0	23.1% CrCl <60 mL/min	100.0	100.0% STEMI	an absolute increase in SCr >0.5 mg/dL after PCI	hospital discharge
Marenzi, Italy, 2009	561	61.2	30.5% CrCl <60 mL/min	100.0	100.0% STEMI	greater than 25% increase in SCr concentration from the baseline value in the 72 hours after primary PCI	hospital discharge
Patti, Italy, 2008	434	65.8	14.5% SCr ≥1.5 mg/dL or CrCl <70 mL/min	100.0	53.2% NSTEMI	postprocedural increase in serum SCr of ≥0.5 mg/dL or >25% from baseline	4 years
Rich, United States, 1990	183	75.4	15.1% SCr >133 µmol/L	23.6	NR	rise in Scr of 44 µmol/L or greater above baseline within 48 hours after catheterization	hospital discharge
Rihal, United States, 2002	7586	65.0	47.7% >1.1 mg/dL	100.0	14.9%	increase in Scr concentration of ≥0.5 mg/dL from pre-procedure values	5 years
Roghi, Italy, 2008	2860	63.0	12.3% eGFR <60 mL/min/1.73m²	100.0	0.0% STEMI	increase in Scr of ≥0.5 mg/dL at 24 h after PCI compared to the pre-procedural value	2 years

Roy, United States, 2008	570	64.8	0.0% (all SCr ≤1.3 mg/dL)	100.0	0.0% AMI	increase in Scr of ≥25% from baseline during hospital stay	6 months
Senoo, Japan, 2010	338	66.0	13.9% SCr >1.1 mg/dL	100.0	94.0% STEMI	Scr increase of 25% from baseline or an absolute increase of ≥0.5 mg/dL that appeared within 2 days	hospital discharge
Skelding, United States, 2007	3213	67.6	38.0% CrCl <60 mL/min	100.0	NR	Scr increase of >1.0 mg/dL from baseline level	hospital discharge
Uyarel, Turkey, 2009	2521	56.5	11.7% eGFR <60 mL/min/1.73m²	100.0	100.0% STEMI	increase in SCr level ≥0.5 mg/dL or ≥25% from baseline within 72h of radiocontrast administration	median 21 months
Weisbord, United States, 2006	27608	63.5	3.2% renal disease based on ICD 9 CM codes	NR	NR	absolute change in SCr from baseline of <0.25, 0.25 to 0.50, 0.51 to 1.0, and >1.0 mg/dL on each of the first 3d after angiography; relative change in Scr or <25, 25-50, 51-100, and >100% on each of the first 3d after angiography	30 days
Weisbord, United States, 2008	181	67.0	100% eGFR <60 mL/min/1.73m²	12.0	NR	increase in SCr ≥25% and ≥0.5 mg/dL	30 days
Wickenbrock, German, 2009	392	64.0	16.3% CrCl <60 mL/min	100.0	100.0% AMI (51.8% STEMI)	absolute increase in SCr >0.5 mg/dL up to 3 days following coronary intervention	hospital discharge
Zaytseva, Russia, 2009	151	57.5	mean eGFR 78.4 mL/min/1.73m²	27.5	NR	absolute increase in SCr of at least 44 µmol/L or by a relative increase of at least 25% over the baseline value in the absence of another cause	1.5 years

Abbreviations: CKD = Chronic Kidney Disease, eGFR = estimated Glomerular Filtration Rate, CrCl = Creatinine Clearance, NR = Not Reported, Scr = Serum Creatinine Concentration, PCI = Percutaneous Coronary Intervention, AMI = Acute Myocardial Infarction, STEMI = ST Segment Elevation MI, ACS = Acute Coronary Syndrome

Table 2.2 – Study Outcomes, Analysis, and Confounders included in Adjustment

Author, Year	Outcomes Included	Study Definition	Adjustment, (Measure of Effect)	Confounders Included
Assali, 2007	Mortality	Death within 30 days of PCI	Logistic regression OR	Age >75 years, renal failure, Killip class, multi-vessel disease, post-TIMI 3, post-diameter stenosis, no-reflow, procedure successful, anti-GP 2B/3A, IABP use, amount of contrast used
Aronow, 2001	Length of Hospital Stay	Days from procedure until discharge	Linear regression Natural logarithm of length of stay	MI 0 to 24 hours, peri-procedure ischemia, intravenous heparin, cerebrovascular accident or transient ischemic attack, women, peripheral vascular disease, , post-procedure IABP, MI 1 to 30 days, post-procedure intravenous nitroglycerin, GI bleeding, repeat angiography, vascular complication, high-risk intervention, arrhythmia, chronic atrial fibrillation, transfusion
Bartholomew, 2004	Major adverse cardiovascular event	Death, AMI, reocclusion during the index hospitalization	Logistic regression OR	Matched by propensity score for CIN including all the following variables: creatinine clearance <60 mL/min, IABP use, Urgent/emergency
	Mortality	Death during the index hospitalization	Logistic regression OR	

				procedure, diabetes mellitus, congestive heart failure, hypertension, peripheral vascular disease, contrast >260 mL
	Length of Hospital Stay	Hospitalization >4 days	Unadjusted RR	None
Bouzas-Mosquera, 2007	Mortality	Mortality on long term follow up	Cox regression HR	age, sex, smoking habit, diabetes mellitus, hypertension, hypercholesterolemia, background of AMI, chronic renal failure, location of the AMI, cardiogenic shock, ejection fraction, multi-vessel disease, success of the procedure, time to revascularization, anemia, fasting blood glucose concentration, maximum troponin I concentration, creatinine concentration ≥1.5 mg/dL, urea concentration ≥50 mg/dL
	Major adverse cardiovascular event	Cardiovascular death, reinfarction, and percutaneous or surgical revascularization with objective evidence of previous myocardial ischemia on long term follow up	Cox regression HR	
	Length of Hospital Stay	Time of hospital stay in days	Unadjusted median	None
Brown, 2008	Mortality	Long term all-cause mortality	Cox regression HR	Age, sex, diabetes, prior myocardial infarction, ejection fraction <35%, non-elective priority, length of post-procedural hospitalization, morbid obesity, prior cardiac

				intervention, baseline eGFR <60 mL/min/1.73m2
	Major adverse cardiovascular event	New AMI, cardiac arrest, coronary stent thrombosis, not including recurrent angina or new congestive heart failure during the index admission	Unadjusted RR	None
	Length of Hospital Stay	Length of hospitalization post procedure	Unadjusted mean	None
Chen, 2008	Mortality	Death from all causes at 6-months follow up	Unadjusted RR	None
Dangas, 2005	Mortality	One year mortality	Logistic regression OR	eGFR, age, female, diabetes, previous AMI, previous CABG, previous PCI, hypertension, NSTEMI, stent used, LVEF <40%, hyperlipidemia, peripheral vascular disease, history of stroke, body surface area, multi-vessel PCI, CHF, NYHA III to IV, pulmonary edema on presentation, hypotension, elective IABP without hypotension, baseline

				hematocrit
	Major adverse cardiovascular event	Death, AMI, target vessel revascularization at 1 year	Unadjusted RR	None
	Length of Hospital Stay	Post-procedure length of stay	Unadjusted mean	None
Ergelen, 2010	Mortality	In-hospital cardiovascular mortality	Logistic regression OR	Unsuccessful procedure, Killip class 2/3, DM, age above 70 years, anemia at admission, multi-vessel disease, female sex, tirofiban use
From, 2008	Mortality	Overall long term mortality	Cox regression HR	heart failure, medications, total hydration, iodine load, prior contrast exposure, age, sex, average prior creatinine value, diabetes mellitus, computed tomography, computed tomographic angiography, noncardiac angiography or venography, coronary catheterization
	Development of ESRD / Chronic Dialysis	Initiation of dialysis >122 days after contrast exposure	Unadjusted RR	None

Goldenberg, 2009	Progression of CKD	Reduction in eGFR	Unadjusted mean	None
	Mortality	Long term all-cause mortality	Cox regression HR	Age, male gender, BMI ≥27, history of hypertension, diabetes mellitus, prior PCI or CABG, LVEF <40, the degree of kidney disease, contrast volume
	Length of Hospital Stay	Length of hospital stay	Unadjusted median	None
Gruberg, 2000	Development of ESRD / Chronic Dialysis	Chronic Dialysis	Unadjusted RR	None
Gupta, 2005	Mortality	Long term all-cause mortality	Cox regression HR	age, gender, LVEF, baseline renal function, worst coronary lesion class, the vessel being intervened on, medication use at time of PCI, AMI
Harjai, 2008	Mortality	Long term all-cause mortality	Cox regression HR	age >65 years, gender, diabetes mellitus, baseline creatinine clearance <60 mL/min, abnormal cardiac biomarkers before PCI
	Major adverse cardiovascular event	Composite of death from any cause, AMI, or target vessel revascularization within 6 months of PCI	Cox regression HR	
Hölscher, 2008	Mortality	Death during the long term follow up period	Cox regression HR	LVEF ≤35%, phosphate, hemoglobin, angiotensin converting enzyme inhibitors, age, diabetes, GFR, loop diuretics

Jabara, 2009	Mortality	In hospital death	Unadjusted RR	None
Kini, 2009	Mortality	1 year mortality	Cox regression HR	Age, sex, cholesterol, BSA, past AMI, chronic pulmonary disease, liver disease, diabetes mellitus, peripheral vascular disease, hypertension, digoxin, coronary lesion type, CK-MB elevation, LVEF, worse AHA/ACC, number of vessels attempted, hemoglobin, troponin I elevation
Kowalczyk, 2007	Mortality	All-cause mortality during long-term follow up	Cox regression HR	age, sex, cardiogenic shock, number of affected coronaries, unsuccessful intervention of infarct related artery, LVEF, hypertension, diabetes, pain duration, previous AMI
Levy, 1996	Mortality	Death during hospitalization	Logistic regression OR	matched on age, baseline serum creatinine, type of contrast study performed and adjusted for: age, sex, race, hypertension, diabetes mellitus, liver disease, acute MI, congestive heart failure, unstable angina, acute infection, sepsis, acute mental status changes, acute stroke, acute leukemia or lymphoma, metastatic cancer, HIV, gastrointestinal bleed, other

				bleed
Lindsay, 2003	Major adverse cardiovascular event	Myocardial Infarction	Logistic regression OR	diabetes mellitus, unstable angina, prior CABG, prior AMI, prior PCI, target vessel revascularization in hospital
	Mortality	1 year all-cause mortality after hospital discharge	Logistic regression OR	age, history of AMI, cerebral or peripheral vascular disease, pulmonary edema
Marenzi, 2004	Length of Hospital Stay	Length of hospital stay	Unadjusted mean	None
Marenzi, 2009	Mortality	Overall in hospital mortality	Unadjusted RR	None
Patti, 2008	Mortality	In hospital death	Unadjusted RR	None
	Major adverse cardiovascular event	Cardiac death, myocardial infarction, or repeat coronary revascularization	Logistic regression OR	Age, sex, statin therapy, diabetes, mellitus, LVEF <40%, balloon angioplasty, stent length <15 mm, stent diameter <3 mm
	Length of Hospital Stay	Length of hospital stay	Unadjusted mean	None
Rich, 1990	Mortality	In hospital death	Unadjusted RR	None
Rihal, 2002	Major adverse cardiovascular event	Myocardial Infarction	Unadjusted RR	None
	Mortality	In hospital death	Logistic regression OR	total volume of contrast medium, age, sex, BMI, Canadian Heart Association class, history of congestive

				heart failure, diabetes, hypertension, peripheral vascular disease, myocardial infarction in the 24 hours before the procedure
Roghi, 2008	Mortality	2 year all-cause mortality	Cox regression HR	age, LVEF, fluoroscopy time, post procedural creatinine kinase-MB ratio, sex, hypertension, diabetes mellitus, dyslipidemia, eGFR, unstable angina, prior MI, heart failure, peripheral vascular disease, atrial fibrillation, CABG, # of coronary arteries with >70% stenosis, severe coronary calcification, type of coronary lesion, acute occlusion, collateral occlusion, angiographic procedural success
Roy, 2008	Major adverse cardiovascular event	composite of death, Q-wave myocardial infarction, and target vessel revascularization	Cox regression HR	age, male gender, hypertension, current smoker, congestive heart failure, BMI, hematocrit, length of procedure, blood transfusion
	Mortality	Death at 30 days	Unadjusted RR	None
	Length of Hospital Stay	Length of hospital stay	Unadjusted mean	None

Senoo, 2010	Mortality	In hospital death	Unadjusted RR	None
Skelding, 2007	Mortality	In hospital death	Logistic regression OR	None
	Length of Hospital Stay	Length of hospital stay	Unadjusted median	None
Uyarel, 2009	Mortality	Long term cardiovascular mortality	Cox regression HR	gender, age ≥75, time to reperfusion >6 h, diabetes mellitus, hypertension, hypercholesterolemia, smoking habit, AMI history, multi-vessel disease, unsuccessful procedure, anterior AMI, cardiogenic shock, admission glucose, anemia
	Major adverse cardiovascular event	Cardiovascular death, reinfarction, target vessel revascularization	Cox regression HR	
	Length of Hospital Stay	Length of hospital stay	Unadjusted mean	None
Weisbord, 2006	Mortality	In hospital death	Logistic regression OR	eGFR, myocardial infarction, congestive heart failure, COPD, diabetes, chronic pulmonary disease, peripheral vascular disease, cerebrovascular disease, renal disease, metastatic solid tumor, rheumatologic disease, peptic ulcer disease, mild liver disease, any malignancy including lymphoma and leukemia, dementia, AIDS
Weisbord,	Mortality	Death within 30 days	Unadjusted	None

2008			RR	
Wickenbrock, 2009	Mortality	In hospital death	Logistic regression OR	Cardiogenic shock, creatinine kinase elevation
	Length of Hospital Stay	Length of hospital stay	Unadjusted mean	None
Zaytseva, 2009	Mortality	Long term mortality	Cox regression HR	Age, sex
	Length of Hospital Stay	Length of hospital stay	Unadjusted mean	None

Abbreviations: OR = Odds Ratio, HR = Hazard Ratio, RR = Risk Ration, AMI = Acute Myocardial Infarction, eGFR = estimated Glomerular filtration rate, CIN = Contrast Induced Nephropathy, BMI = Body Mass Index, LVEF = Left Ventricular Ejection Fraction, IABP = Intra-Arterial Balloon Pump, PCI = Percutaneous Coronary Intervention, NYHA = New York Heart Association, CABG = Coronary Artery Bypass Graft

Table 2.3 – Study Quality Assessment

Author, Year	Inclusion / Exclusion Criteria Specified	Inclusion of Consecutive Patients	Losses to Follow-Up	Outcome Assessment Blinded to Exposure Status	Adjustment For Confounders
Assali, 2007	Yes	Yes	0%	NR	Mortality - Yes
Aronow, 2001	Yes	Yes	0%	NR	LOS - Yes
Bartholomew, 2004	Yes	Yes	0%	NR	Mortality - Yes, CV events - Yes, LOS - No
Bouzas-Mosquera, 2007	Yes	Yes	0%	NR	Mortality - Yes, CV events - Yes, LOS - No
Brown, 2008	Yes	Yes	0%	NR	Mortality - Yes, CV events - No, LOS - No
Chen, 2008	Yes	Yes	0%	NR	Mortality - No
Dangas, 2005	Yes	Yes	0%	Yes	Mortality - Yes, CV events - No, LOS - No
Ergelen, 2010	Yes	Yes	0%	NR	Mortality - Yes
From, 2008	Yes	Yes	0%	NR	Mortality - Yes, ESRD - No
Goldenberg, 2009	Yes	Yes	4% for CKD, 0% for mortality follow-up	NR	Mortality - Yes, LOS – No, Progression of CKD - No
Gruberg,	Yes	Yes	0%	NR	ESRD - No

2000					
Gupta, 2005	Yes	Yes	0%	NR	Mortality - Yes
Harjai, 2008	Yes	Yes	0%	NR	Mortality - Yes, CV events - Yes
Hölscher, 2008	Yes	Yes	0%	NR	Mortality - Yes
Jabara, 2009	Yes	Yes	0%	NR	Mortality - No
Kini, 2009	Yes	Yes	0%	NR	Mortality - Yes
Kowalczyk, 2007	Yes	Yes	0%	No	Mortality - Yes
Levy, 1996	Yes	Yes	0%	NR	Mortality - Yes
Lindsay, 2003	Yes	Yes	17%	NR	Mortality - Yes, CV events - Yes
Marenzi, 2004	Yes	Yes	0%	NR	LOS - No
Marenzi, 2009	Yes	Yes	0%	NR	Mortality - No
Patti, 2008	Yes	Yes	0.9%	NR	Mortality - No, CV events - Yes, LOS - No
Rich, 1990	Yes	Yes	0%	NR	Mortality - No
Rihal, 2002	Yes	Yes	0%	NR	Mortality - Yes, CV events - No
Roghi, 2008	Yes	Yes	0%	NR	Mortality - Yes
Roy,	Yes	Yes	0%	Yes	Mortality - No, CV events - Yes,

2008					LOS - No
Senoo, 2010	Yes	Yes	0%	NR	Mortality - No
Skelding, 2007	Yes	Yes	0%	NR	Mortality - No, LOS - No
Uyarel, 2009	Yes	Yes	2%	NR	Mortality - Yes, CV events - Yes, LOS - No
Weisbord, 2006	Yes	Yes	0%	NR	Mortality - Yes
Weisbord, 2008	Yes	Yes	0%	NR	Mortality - No
Wickenbrock, 2009	Yes	Yes	0%	NR	Mortality - Yes, LOS - No
Zaytseva, 2009	NR	NR	NR	NR	Mortality - Yes, LOS - No

Abbreviations: NR = Not Reported, LOS = Length of Stay, CV = Cardiovascular

Figure 2.1 – Study Selection Flowchart

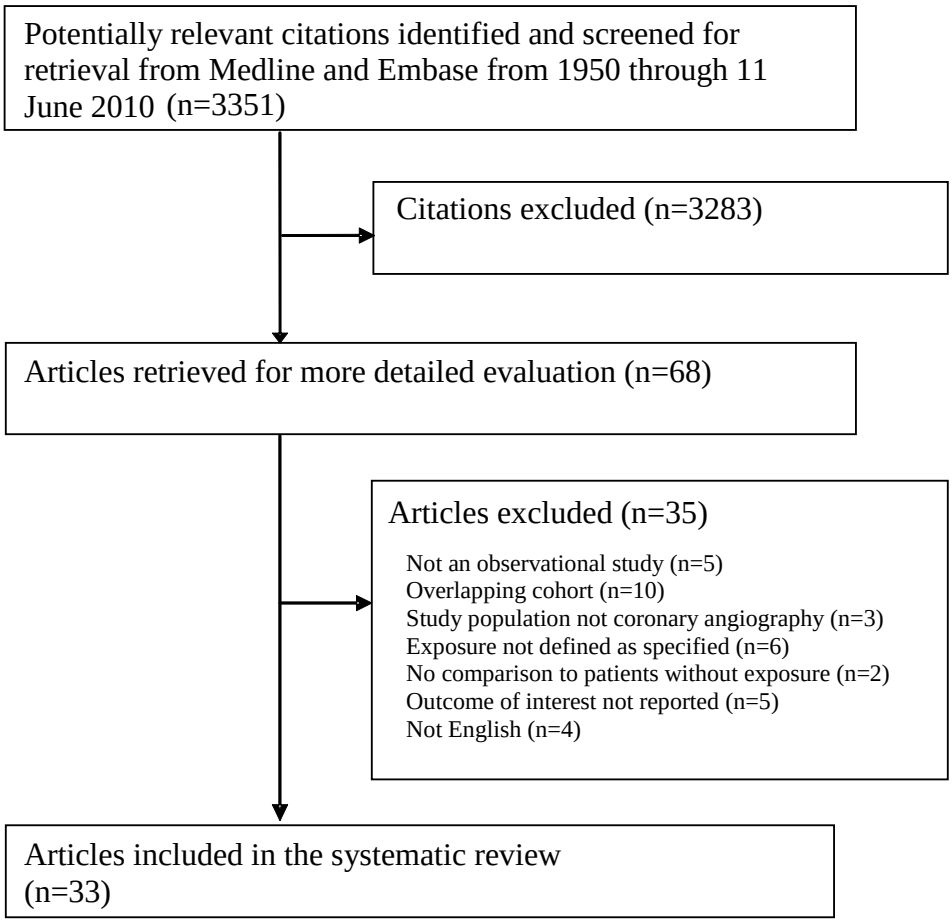
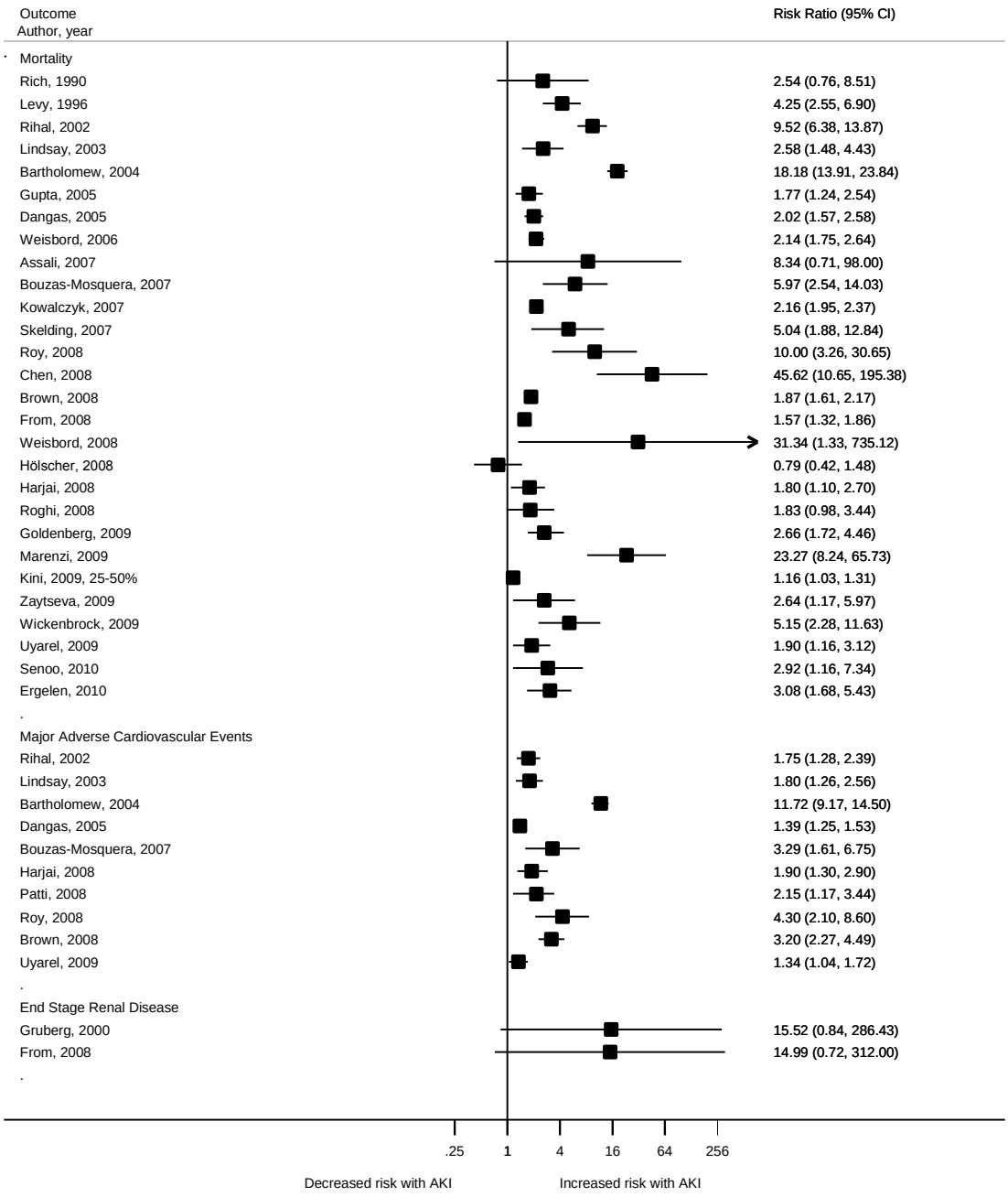
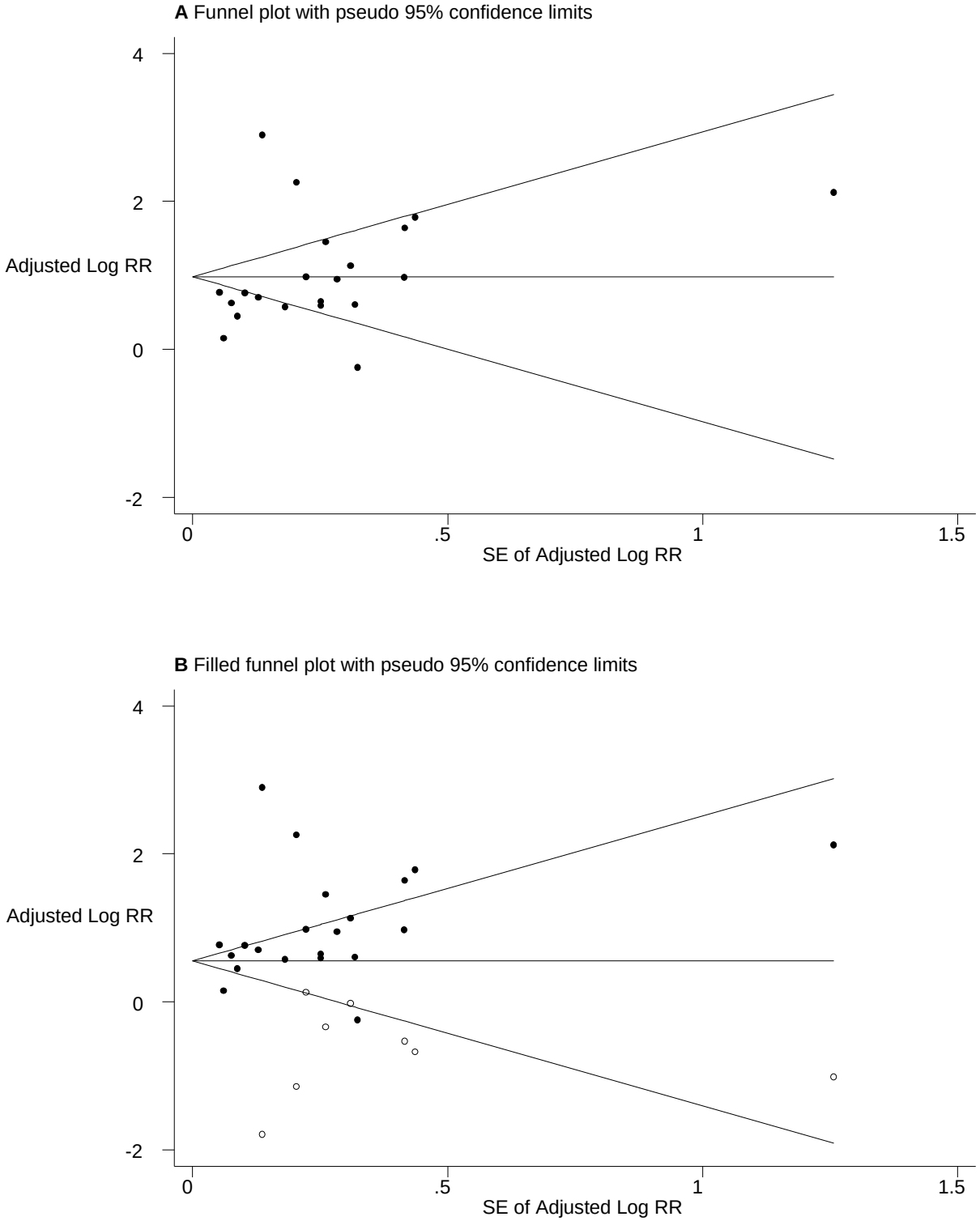


Figure 2.2 – Relative Risks of Mortality, Cardiovascular Events, and End-stage Renal Disease Associated with Acute Kidney Injury after Coronary Angiography



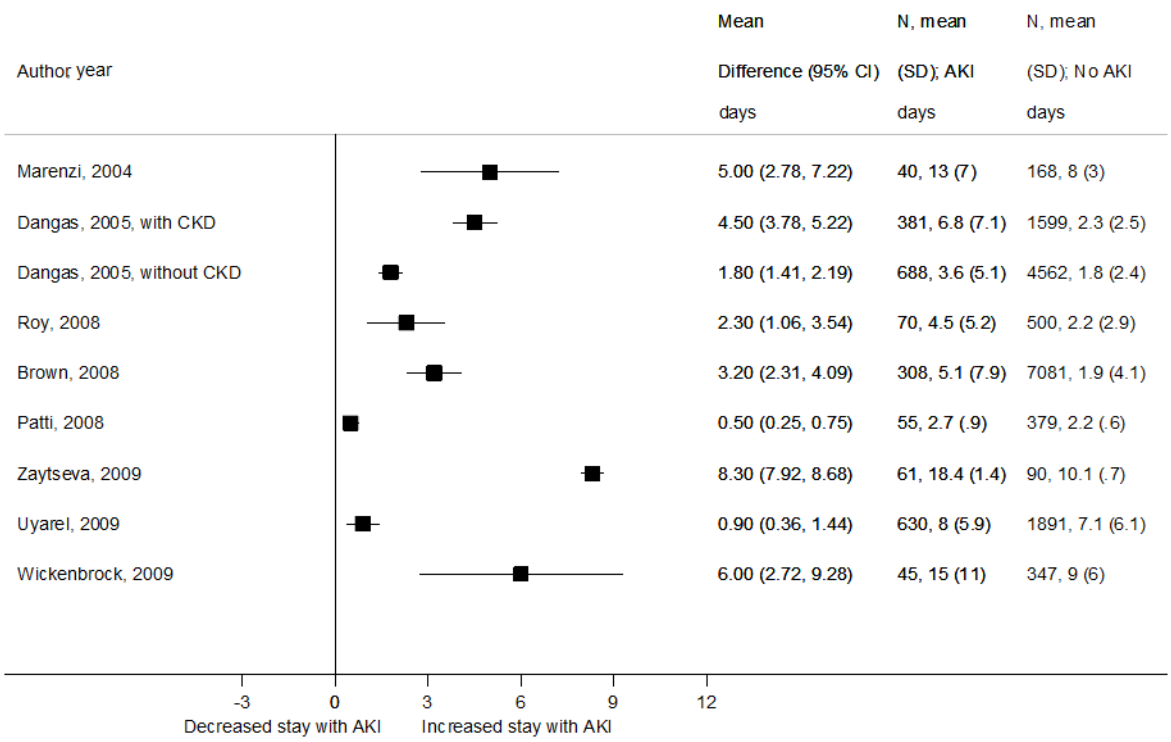
Black squares indicate point estimates and horizontal lines indicate 95% CIs, for each study.
Abbreviations: CI = Confidence Interval, AKI = Acute Kidney Injury

Figure 2.3 – Funnel Plot Before (A) and After Trim and Fill Procedure (B)



Solid circles represent identified studies, open circles represent hypothesized unpublished studies from trim and fill procedure. Abbreviations: RR = Risk Ratio, CI = Confidence Intervals, SE = Standard Error

Figure 2.4 – Weighted Mean Difference in Hospital Length of Stay Associated with Acute Kidney Injury after Coronary Angiography



Black squares indicate point estimates, horizontal lines indicate 95% CIs, and grey boxes indicate the weight for each study.
Abbreviations: CI = Confidence Interval, AKI = Acute Kidney Injury

Chapter Three: Acute Kidney Injury and Long-term Decline in Kidney Function Following Coronary Angiography

3.1 Abstract

Background **-** Acute kidney injury is common after coronary angiography; however, its long-term effects on kidney function are unclear.

Methods **-** We performed a cohort study examining long-term changes in kidney function in adults undergoing coronary angiography in the province of Alberta, Canada between 2004 and 2006. Eligible subjects were those who had serum creatinine measurements as part of their clinical care. Acute kidney injury was categorized by the magnitude of increase in serum creatinine (mild [50 – 99% or ≥ 0.3 mg/dL (26.4 μmol/L)], moderate or severe [≥ 100%]) within 7 days of coronary angiography.

Results **-** Compared to patients without acute kidney injury, the adjusted odds of a decline in kidney function at 3 months after angiography increased more than 4-fold for subjects with mild acute injury (Odds Ratio 4.74, 95% Confidence Interval [CI] 3.92, 5.74), and more than 17-fold for those with moderate or severe acute kidney injury (Odds Ratio 17.31, 95% CI 12.03, 24.90). Among those with an estimated glomerular filtration rate < 90 mL/min/1.73m^2 after angiography, the subsequent adjusted mean rate of decline in estimated glomerular filtration during long-term follow-up was 0.2 (95% CI -0.4, 0.8) mL/min/1.73m^2/year in patients without acute kidney injury, 0.8 (95% CI 0.1, 1.6) mL/min/1.73m^2/year following mild acute kidney injury, and 2.8 (95% CI 1.7, 4.1) mL/min/1.73m^2/year following moderate to severe acute kidney injury.

Conclusion **-** Acute kidney injury following coronary angiography is associated with a sustained loss and larger rate of future decline in kidney function than occurs in patients who do not suffer AKI.

3.2 Introduction

Acute kidney injury (AKI) following coronary angiography is often transient, with improvement in kidney function observed within days to weeks[21;24;25]. Although severe AKI that requires dialysis is a rare event in this setting[26;27], even AKI of lesser severity has been consistently associated with adverse outcomes including death[15;95]. Patients with pre-existing chronic kidney disease (CKD) constitute a high risk group for AKI in the setting of radiocontrast administration[21]. Furthermore, CKD itself is associated with graded increases in risk of mortality with incremental reductions in glomerular filtration rate (GFR)[41;113;114]. These observations suggest that the long-term effects of AKI on the development and progression of CKD are important to understand.

The long-term trajectory of kidney function following an episode of AKI remains unclear. The majority of what is currently known relates to the risk of developing end-stage renal disease (ESRD) requiring dialysis among survivors of severe AKI[59;115;116]. The effects of lesser degrees of AKI have not been characterized, nor have the long-term effects of AKI on kidney function based on the rate of decline in estimated GFR after hospital discharge. Furthermore, the effects of AKI on serial post-procedure measurements of kidney function have not been examined following coronary angiography specifically, an event which is particularly relevant given the high cardiovascular risk and use of this procedure in patients with or at risk for CKD. Identification of patients at high risk for progressive loss of kidney function after these procedures would provide important prognostic information to guide subsequent patient care.

The purpose of this study was to examine the association between AKI and long-term changes in kidney function following coronary angiography. We hypothesized that a graded association would exist between the severity of an AKI episode and loss of kidney function at 3 months post-angiography. We also hypothesized that AKI would be an independent predictor of the subsequent rate of decline in GFR beyond 3 months following coronary angiography.

3.3 Methods

3.3.1 Study population

The study cohort was derived from the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH), a prospective data collection initiative that captures detailed clinical information on all patients undergoing coronary angiography in Alberta, Canada at the time of their procedure[68]. Coronary angiography was performed using non-ionic iodinated radiocontrast agents with the choice of low- or iso-osmolar radiocontrast agents and use of N-acetylcysteine and intravenous fluid made at the discretion of treating physicians.

The cohort consisted of all Alberta residents, ≥ 18 years of age, undergoing coronary angiography from 1 January 2004 to 31 December 2006 in Alberta. To be eligible for inclusion, participants required at least one serum creatinine measurement obtained from an outpatient laboratory in each of two time periods relative to the coronary angiogram: within a 6 month period preceding the coronary angiogram; and > 3 months following the

angiogram (Figure 1). Patients with a renal transplant or who were receiving dialysis prior to coronary angiography were excluded based on linkage with the Northern and Southern Alberta Renal Program registries[117] or by physician billing claims (*Canadian Classification of Procedures* codes 13.99A, 13.99B, 13.99C, 13.99D, and 13.99O)[118]. Patients undergoing coronary artery bypass surgery (CABG) within 7 days of coronary angiography were excluded to minimize causes of AKI other than those related to angiography. The cohort entry date for each patient was the date of the first coronary angiogram performed during the study period.

3.3.2 Measurement of exposure

All serum creatinine measurements made in Alberta outpatient facilities, or inpatient facilities that perform coronary angiography, were obtained from the Alberta Kidney Disease Network repository of laboratory data[119]. AKI was defined based on the change in serum creatinine concentration from the last pre-angiogram level to the peak level observed within 7 days following the coronary angiogram. We defined mild AKI as an increase in serum creatinine of 50 – 99% or by ≥ 0.3 mg/dL (26.4 μmol/L), and moderate or severe AKI as an increase in serum creatinine ≥ 100%[12]. Patients with no creatinine measurements within 7 days post angiography with which to ascertain AKI were excluded.

3.3.3 Measurement of kidney function

The 4-variable Modification of Diet in Renal Disease (MDRD) Study equation[120] was used to estimate eGFR prior to coronary angiography and beyond 3 months following

angiography (Figure 3.1). Although data on race was not available, misclassification of eGFR was expected to be minimal as < 1% of the Alberta population is black[119]. During the study period several Alberta laboratories switched from non-standardized creatinine assays to isotope dilution mass spectroscopy (IDMS) calibrated serum creatinine assays[121]; we used the non-IDMS traceable MDRD study equation as well as the IDMS-traceable MDRD study equation to determine eGFR as appropriate based on the laboratory and date of creatinine measurement[122]. To reduce inter-laboratory variation in eGFR, creatinine measurements were standardized across provincial laboratories to an IDMS reference standard, and a laboratory-specific correction factor was applied as previously described[119].

3.3.4 Measurement of covariates

Age, sex, comorbidities, and information on coronary revascularization procedures (percutaneous coronary intervention [PCI] and CABG) were determined from the APPROACH database. Pre-angiography eGFR was estimated using the last available outpatient creatinine measurements made within 6 months prior to coronary angiography. Post-angiography eGFR was calculated using the first available outpatient creatinine measurement made > 3 months after angiography. Provincial laboratory data was used to obtain all outpatient urine protein results collected prior to angiography[119]. Urine protein was categorized as absent, microalbuminuria or macroalbuminuria / proteinuria as previously described [123]. Classification was based on the most recent pre-angiography urine specimen for patients with 2 measurements, and based on the median result when ≥ 3 measurements were available.

3.3.5 Measurement of Outcomes

Participants were followed until death (identified from Alberta Vital Statistics Registry), the date of registration for chronic dialysis or renal transplantation (identified from the Northern or Southern Alberta Renal Program databases), or the study end date (31 December, 2007). We considered a sustained loss of kidney function to be present after coronary angiography when the lowest serum creatinine concentration obtained between 7 days to 3 months post-angiography was more than 50% or 0.3 mg/dL (26.4 μmol/L) greater than the last pre-angiography measurement [124] [13]. The subsequent decline in kidney function occurring beyond 3 months following angiography was assessed for patients with a post-angiography eGFR < 90 mL/min/1.73m^2 (captured > 3 months following the angiogram) and was based upon the annual rate of decline in eGFR during the remaining follow-up period[125]. To address the effect that AKI may have on acceleration of progression of kidney function, we compared the rate of decline in eGFR in periods before and after coronary angiography in the subgroup of these patients who also had eGFR measurements that spanned a minimum of 1 year during the pre-angiography time period[126]. Rapid progression of kidney disease, defined as a rate of decline in eGFR > 4 mL/min/1.73m^2/year[127] or the initiation or chronic renal replacement therapy (dialysis or renal transplant) during the follow-up period beyond 3 months after coronary angiography, was also identified.

3.3.6 Statistical analysis

Differences in baseline characteristics according to AKI status were compared using analysis of variance or Chi-squared tests as appropriate. Logistic regression models including terms for covariate in Table 3.1 were fit to determine the association between AKI and decline in kidney function at 3 months. For patients with post-angiography eGFR < 90 mL/min/1.73m^2, further progression of kidney dysfunction according to the annual rate of decline in eGFR in ml/min/1.73m^2 was determined using mixed effects models with random intercepts and random slopes. These models estimate the rate of change in eGFR as a linear function over time, taking into account the varying number and spacing of measurements of eGFR as well as the variable follow-up for each subject, and avoid high variability in estimates for patients with short follow-up[128;129]. All outpatient eGFR measurements obtained more than 3 months after coronary angiography until death, initiation of renal replacement therapy, or the study end-date were included in these models which were adjusted for age, sex, proteinuria, and comorbidities. In a subgroup analysis, the mixed effects model was expanded to include pre-angiography estimates of eGFR, incorporating a fixed effect to assess differences in the annual rate of change in eGFR in the pre- and post-angiography time periods. Logistic regression models were used to determine the association between AKI and the risk of rapid progression occurring > 3 months after angiography in patients with post-angiography eGFR < 90 mL/min/1.73m^2. Stepwise elimination and backward selection were used to select variables for inclusion in the final logistic regression and mixed effects models. The normal distribution of random effects for the mixed effects model and linearity of the logit for logistic regression models were tested using graphical approaches. All statistical

analyses were conducted using STATA (version 10.0; STATA Corp., College Station, TX). The conjoint health research ethics board of the University of Calgary approved the study.

3.4 Results

3.4.1 Cohort formation and characteristics

We identified 19,022 Alberta residents 18 years of age or older undergoing coronary angiography with ≥ 1 outpatient serum creatinine measurement made in both the pre- and greater than 3 month post-angiography time periods. We excluded 327 patients receiving renal replacement therapy prior to study entry, and 616 patients who underwent CABG surgery within 7 days following angiography. Of the remainder, 11,249 (62.2%) had a serum creatinine measurement within 7 days following coronary angiography, and were included in the final cohort (Figure 3.2).

The mean age of the cohort was 63.6 years, 69.6% were male, and the mean eGFR prior to coronary angiography was 73.8 mL/min/1.73m^2. A total of 853 participants (7.6%) developed AKI following coronary angiography; 716 (6.4 %) with mild AKI (increase in serum creatinine 50 – 99% or by ≥ 0.3 mg/dL [26.4 μmol/L]), and 137 (1.2%) with moderate or severe AKI (increase in serum creatinine ≥ 100%). Patients who developed AKI were older, more likely to be women, with lower pre-angiography eGFR, proteinuria, and were more likely to have comorbidities including diabetes mellitus, hypertension, and heart failure (Table 3.1).

Median follow-up from the date of coronary angiography was 2.5 years (interquartile range [IQR] 2.2 – 2.8 years). The median number of serum creatinine measurements obtained between 7 days and 3 months post-angiography was 6 (IQR 4, 9), while the median number of outpatient serum creatinine measurements obtained > 3 months post-angiography was 3 (IQR 2, 4), with a median interval between measurements of 7 months (IQR 1, 11 months). During follow-up beyond 3 months after coronary angiography, 638 participants (5.7 %) died, while 46 (0.4 %) initiated chronic renal replacement therapy.

3.4.2 Loss of kidney function at 3 months following coronary angiography

The proportion of patients with a sustained loss of kidney function (serum creatinine concentration > 50% or 0.3 mg/dL [26.4 μmol/L] above pre-angiography concentration > 3 months following the procedure) increased with greater severity of AKI, occurring in 5.9% of patients without AKI, 28.2% of patients with mild AKI, and 59.1% among patients with moderate or severe AKI (Table 3.2). In the final model adjusted for age, sex, pre-angiography eGFR, proteinuria, comorbidities, and revascularization procedures, compared to patients without AKI, the odds of a decline in kidney function by 3 months increased more than 4 fold for subjects with mild AKI Stage (Odds Ratio [OR] 4.74, 95% Confidence Interval [CI] 3.92 – 5.74), and more than 17-fold for those with moderate or severe AKI (OR 17.31, 95% CI12.03 – 24.90).

3.4.3 Long-term decline in kidney function following coronary angiography

Among the 10,418 (92.6%) patients with a post-angiography eGFR < 90 mL/min/1.73m^2 more than 3 months following angiography, those who had developed AKI had lower

eGFR at 3 months, as well as further decline in eGFR during subsequent long-term follow-up (Figure 3.3). The unadjusted mean annual rate of decline in eGFR during long-term follow-up was 0.1 (95% CI -0.1, 0.2) mL/min/1.73m^2/year among patients without AKI, 1.0 (95% CI 0.4, 1.5) mL/min/1.73m^2/year among patients with mild AKI, and 3.1 (95% CI 2.0, 4.2) mL/min/1.73m^2/year among patients with moderate or severe AKI. After adjustment for age, sex, proteinuria, and comorbidities, the adjusted rate of decline in eGFR was 0.2 (95% CI -0.4, 0.8) mL/min/1.73m^2/year in patients without AKI, 0.8 (95% CI 0.1, 1.6) mL/min/1.73m^2/year in those who had developed mild AKI, and 2.8 (95% CI 1.7, 4.1) mL/min/1.73m^2/year in patients who had experienced moderate to severe AKI (p-trend < 0.001). The odds of rapid progression of kidney disease during the long term follow-up period also increased in a graded manner with increasing severity of AKI (Table 3.3). The test for interaction between AKI and post-angiogram eGFR was non-significant (p-interaction 0.24) suggesting that AKI was associated with similar risks of subsequent rapid progression of kidney disease regardless of the eGFR at the start of long-term follow-up.

3.4.4 Comparison of pre- and post-angiography rates of decline in kidney function

There were 5,478 (59.2%) patients who also had estimates of GFR available spanning > 1 year prior to angiography with which to estimate the pre-angiography rate of decline in kidney function. The annual rate of decline in eGFR was similar for the pre- and the post-angiography time periods for patients without AKI or with mild AKI. For patients who experienced moderate or severe AKI, there was a statistically significant increase in the

rate of decline in kidney function following the episode of AKI by 1.8 (95% CI 0.6 – 3.0) mL/min/1.73m^2/year, compared to the pre-angiography rate.

3.4.5 Sensitivity analyses

Sensitivity analyses were conducted to explore the impact of the number and frequency of serum creatinine measurements on results. For the analysis of kidney function at 3 months, we restricted the cohort to patients who had ≥ 2 creatinine measurements obtained between 7 days and 3 months following angiography, which produced similar findings to our primary analysis. For the analysis of long-term progression of kidney function beyond 3 months following angiography, we stratified the cohort according to the number of serum creatinine measurements during the follow-up period (≤ 2, 3, or ≥ 4 measurements). Although the subsequent rate of decline in eGFR increased with greater number of serum creatinine measurements across all categories of AKI, the relative increases in rate of decline in eGFR, and odds of rapid progression with mild and moderate or severe AKI were comparable across all strata to those observed in the primary analyses.

3.5 Discussion

In this large cohort undergoing coronary angiography, a loss of kidney function at 3 months following coronary angiography was common after AKI. Among patients with an eGFR < 90 mL/min/1.73m^2 following angiography, the long-term risk of further progressive loss of kidney function also increased with greater severity of AKI. Furthermore, patients with moderate or severe AKI experienced acceleration in the rate

of eGFR decline following an episode of AKI compared to their pre-angiography rate of progression. These results demonstrate that patients who develop AKI following coronary angiography are at increased risk for progressive long-term loss of kidney function following angiography.

Although the short-term adverse effects of AKI during hospitalization are well recognized[15;16;34], the long-term effects of AKI on renal outcomes have been unclear because comparisons to patients without AKI have been lacking, the confounding effects of pre-existing CKD have not been controlled for, or identification of progression of kidney disease has been based solely on receipt of treatment for ESRD[126;130]. Elderly patients hospitalized with diagnosis codes for AKI superimposed on CKD[115], as well as patients with increases in creatinine following hospitalization with myocardial infarction have been demonstrated to be at increased risk for enrollment in ESRD programs in the United States[66]. Severe AKI leading to dialysis during hospitalization has recently been shown to be associated with an increased risk for chronic renal replacement therapy in later life [59;131], while patients with diagnosis codes for acute tubular necrosis or dialysis-requiring AKI have also been reported to be at risk for earlier identification of stage 4 or 5 CKD[132;133].

This analysis expands upon the findings of previous studies by identifying both AKI and subsequent changes in kidney function using serial measurements of serum creatinine and eGFR. This is a significant advantage given the limitations in sensitivity and specificity when using administrative codes to define AKI and CKD in isolation or combination [134-

[136]. Furthermore, the use of pre- and post-angiography estimates of GFR allowed for the confounding effects of pre-existing CKD (and its severity) to be accounted for in these analyses [126].

A number of mechanisms may explain the associations between AKI and progressive loss of kidney function following coronary angiography. First, the association may be due to numerous comorbidities (i.e. hypertension, diabetes mellitus, proteinuria, or more advanced pre-existing CKD) in patients who develop AKI. However, the magnitude of the associations that remained after statistical adjustment suggest that confounding by these characteristics are unlikely to explain our findings. Second, patients who develop AKI may be more likely to have a serum creatinine measurement obtained during follow-up, thus introducing potential for ascertainment bias. However, we observed similar results when analyses were stratified by the number of serum creatinine measurements performed during follow-up, suggesting that the clinical decisions that lead to the measurement of serum creatinine do not explain our findings. Third, patients who develop AKI may be susceptible to other processes that lead to progressive kidney disease following angiography such as atheroemboli[137]. Alternatively, the long-term decline in eGFR following AKI may be due to persisting renal damage after an episode of acute tubular injury. Animal studies suggest that chronic changes to the renal microvasculature may result from acute ischemic renal injury[62;138]. Our observations that kidney function was less likely to recover to pre-angiography levels, and further declined at a faster rate following an episode of AKI are in keeping with this hypothesis.

There are limitations to our study resulting from its observational nature and the use of serum creatinine and eGFR to determine kidney function. First, because this study was conducted retrospectively, participant selection was limited to patients who had pre- and post-angiography serum creatinine measurements including measurements within 7 days of coronary angiography as part of their clinical care. Although many outpatients were thus excluded because of the inability to ascertain AKI, these patients had few risk factors for AKI and exhibited a low rate of CKD progression during follow-up (decline in eGFR 0.1 mL/min/1.73m^2/year). Therefore exclusion of these patients from the study and restriction of the control group to those with creatinine measurements are unlikely to have impacted our findings. Second, episodes of AKI and their severity may have been misclassified due to our dependence on existing creatinine measurements captured following coronary angiography. However, our approach to identification of AKI is most vulnerable to missing episodes of mild AKI or underestimating the severity of AKI in those who developed it. If such misclassification occurred, we anticipate this would have underestimated the risk of renal outcomes following moderate or severe AKI. Finally, measurement of long-term study outcomes required that patients survive beyond 3 months to obtain repeated measures of kidney function. Loss of patients due to death, ESRD, or loss to clinical follow-up may thus have influenced results. However, because patients with more rapid decline in kidney function are more likely to experience death or ESRD[127;139], our estimates of the rate of progression are likely conservative [140].

The associations between AKI and progressive kidney dysfunction have potentially important implications for clinical management of patients following coronary

angiography, given the availability of strategies that may slow the progression of CKD [141;142]. Our findings suggest a need for clinical follow-up and further research evaluating strategies to reduce progression of kidney disease in patients developing AKI following angiographic procedures.

In conclusion, patients with AKI are at increased risk of sustaining a loss of kidney function following coronary angiography, and further decline in kidney function during long-term follow-up. Patients who develop AKI following coronary angiography should be considered at increased risk for progressive kidney disease and its associated complications. Further research should focus on the effects of interventions to slow the progression of CKD in survivors of radiocontrast associated AKI.

Table 3.1 - Characteristics of patients undergoing coronary angiography, according to Acute Kidney Injury status.

	No AKI (n=10,396)	Mild AKI (n=716)	Moderate or Severe AKI (n=137)	p-value †
Age, yr, mean (SD)	63.3 (12.2)	68.3 (11.8)	66.8 (12.0)	<0.0001
Sex, male, No. (%)	7,263 (69.9)	490 (68.4)	79 (57.7)	0.007
Pre-angiography eGFR, mL/min/1.73m^2, Mean (SD):	74.0 (19.8)	62.4 (24.3)	61.8 (26.2)	<0.0001
Pre-angiography eGFR, Categories, No. (%):				
≥ 90 mL/min/1.73m^2	1,897 (18.2)	84 (11.7)	16 (11.7)	<0.001
60 – 89 mL/min/1.73m^2	6,195 (59.6)	280 (39.1)	49 (35.8)	
30 – 59 mL/min/1.73m^2	2,196 (21.1)	315 (44.0)	59 (43.1)	
< 30 , mL/min/1.73m^2	108 (1.0)	37 (5.2)	13 (9.5)	
Proteinuria, No (%):				
Absent	6,779 (65.2)	424 (59.2)	71 (51.8)	<0.001
Microalbuminuria	1,225 (11.8)	161 (22.5)	50 (36.5)	
Proteinuria	40(3.8)	11 (1.5)	1 (0.7)	
Unmeasured	2,352 (22.6)	120 (16.8)	15 (10.9)	
Comorbidities, No (%):				
Diabetes mellitus	2,730 (26.3)	265 (37.0)	62 (45.2)	<0.001
Hypertension	7,024 (67.6)	537 (75.0)	93 (67.9)	<0.001
Hyperlipidemia	8,098 (77.9)	538 (75.1)	90 (65.7)	0.001
Heart failure	1,450 (13.9)	224 (31.3)	60 (43.8)	<0.001
Cerebrovascular disease	751 (7.2)	83 (11.2)	25 (18.2)	<0.001
Peripheral vascular disease	786 (7.6)	84 (11.7)	20 (14.6)	<0.001
Chronic pulmonary disease	1,709 (16.4)	190 (26.5)	29 (21.1)	<0.001
Liver disease	141 (1.4)	14 (2.0)	5 (3.6)	0.014
Malignancy	451 (4.3)	41 (5.7)	8 (5.8)	0.16
Current smoker	3,030 (29.1)	166 (23.2)	25 (18.2)	<0.001
Procedures following diagnostic angiogram, No (%):				
Percutaneous coronary intervention	5,356 (51.5)	329 (45.9)	50 (36.5)	<0.001
Coronary artery bypass surgery	1,335 (12.8)	112 (15.6)	21 (15.3)	0.072

† ANOVA or Chi squared test. Abbreviations: AKI = Acute Kidney Injury, SD = Standard deviation

Table 3.2 – Sustained loss of kidney function at 3 months following coronary angiography

	No AKI	Mild AKI	Moderate or Severe AKI
No. patients	10,396	716	137
No. serum creatinine measurements per patient, Median (IQR)	6 (3, 9)	8 (5, 14)	7 (4, 17)
Decline in kidney function‡:			
No. (%)	613 (5.9%)	202 (28.2%)	81 (59.1%)
Crude Odds Ratio (95% CI)	1 [Reference]	6.30 (5.25, 7.56)	23.20 (16.34, 32.94)
Adjusted Odds Ratio (95% CI)*	1 [Reference]	4.74 (3.92, 5.74)	17.31 (12.03, 24.90)

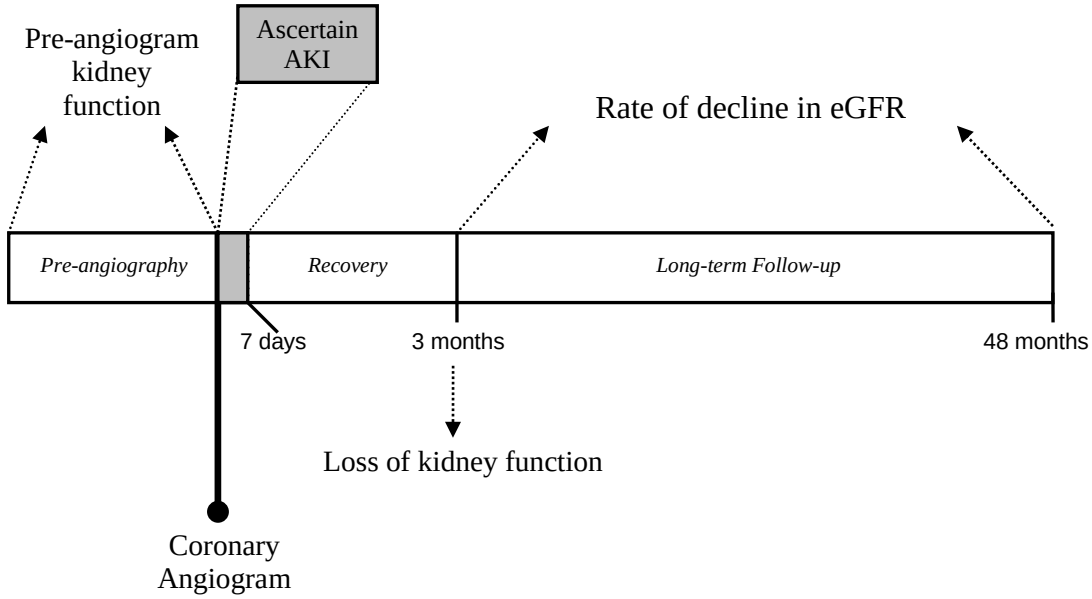
‡ Loss of kidney function = serum creatinine > 50% or 0.3 mg/dL (26.4 μmol/L) above pre-angiography concentration on all measurements obtained 7 days to 3 months following angiogram.
*Final model adjusted for age, sex, pre-angiography eGFR, proteinuria, comorbidities (diabetes mellitus, hypertension, heart failure, cerebrovascular disease, chronic pulmonary disease), revascularization following coronary angiogram (percutaneous coronary intervention or coronary artery bypass surgery).
Abbreviations: OR=Odds Ratio, CI=Confidence Interval, AKI=Acute Kidney Injury

Table 3.3 – Long-term changes in kidney function beyond 3 months following coronary angiography among patients with post-angiography eGFR < 90 mL/min/1.73m^2, according to Acute Kidney Injury status.

	No AKI	Mild AKI	Moderate or Severe AKI
No. patients	9,565	716	137
eGFR 3 months post-angiography, mL/min/1.73m^2 (95% CI)	66.0 (65.7, 66.3)	53.4 (50.1, 52.7)	51.5 (48.8, 54.1)
Follow-up duration, months, Median (IQR)	21.8 (13.0, 30.8)	20.4 (12.8, 30.1)	22.5 (13.4, 30.4)
No. serum creatinine measurements per patient, Median (IQR)	3 (1, 5)	4 (2, 8)	4 (2, 10)
Rate of decline in eGFR (mL/min/1.73m^2/year):			
Crude Mean (95% CI)	0.1 (-0.1, 0.2)	1.0 (0.4, 1.5)	3.1 (2.0, 4.2)
Adjusted Mean (95% CI)†	0.2 (-0.4, 0.8)	0.8 (0.1, 1.6)	2.8 (1.7, 4.1)
Rapid progression of kidney disease:			
Decline in eGFR > 4 mL/min/1.73m^2/year, No. (%)	333 (3.4%)	58 (7.8%)	22 (16.0%)
Initiated chronic renal replacement therapy, No (%)	21 (0.2%)	18 (2.4%)	8 (5.8%)
Composite outcome*			
Crude Odds Ratio (95% CI)	1 [Reference]	2.81 (2.15, 3.67)	6.52 (4.22, 10.07)
Adjusted Odds Ratio (95% CI)‡	1 [Reference]	1.60 (1.19, 2.14)	3.12 (1.95, 4.99)

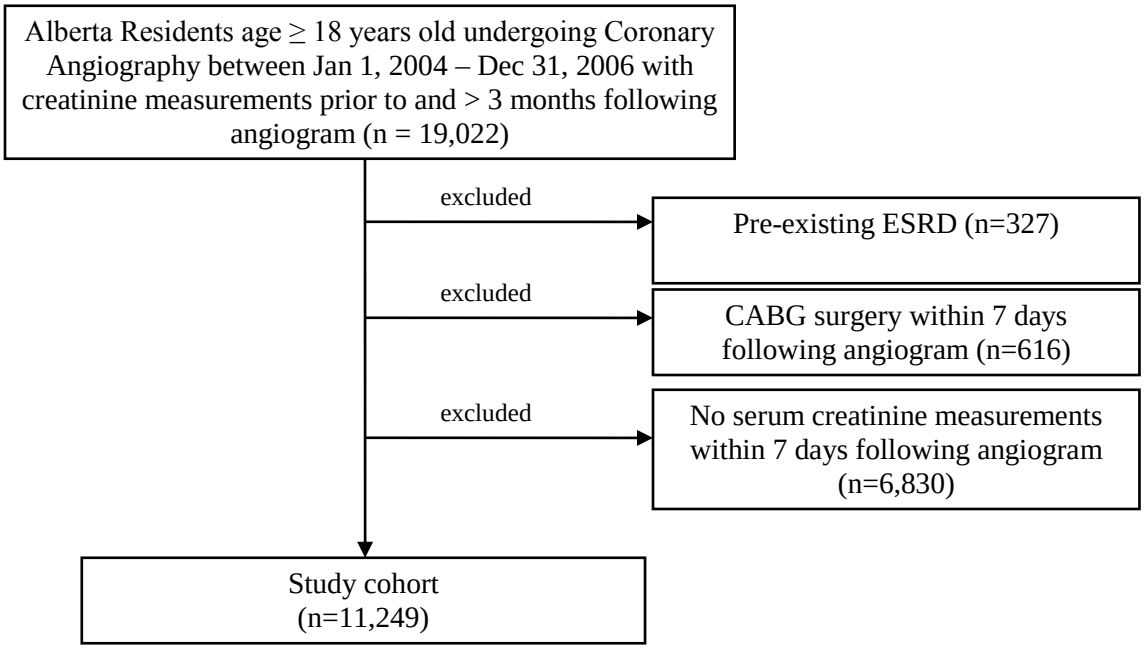
*Composite outcome = Decline in eGFR > 4mL/min/1.73m^2/year or initiation of chronic renal replacement therapy.
†Final model adjusted for age, sex, and comorbidities (diabetes mellitus, hypertension, proteinuria, and heart failure).
‡Final model adjusted for age, sex, baseline eGFR, proteinuria, comorbidities (diabetes mellitus, hypertension, heart failure, cerebrovascular disease, peripheral vascular disease, chronic pulmonary disease, liver disease, malignancy, and current smoking).
Abbreviations: AKI = Acute Kidney Injury, eGFR = estimated Glomerular Filtration Rate, IQR = Interquartile Range

Figure 3.1 – Overview of study design.



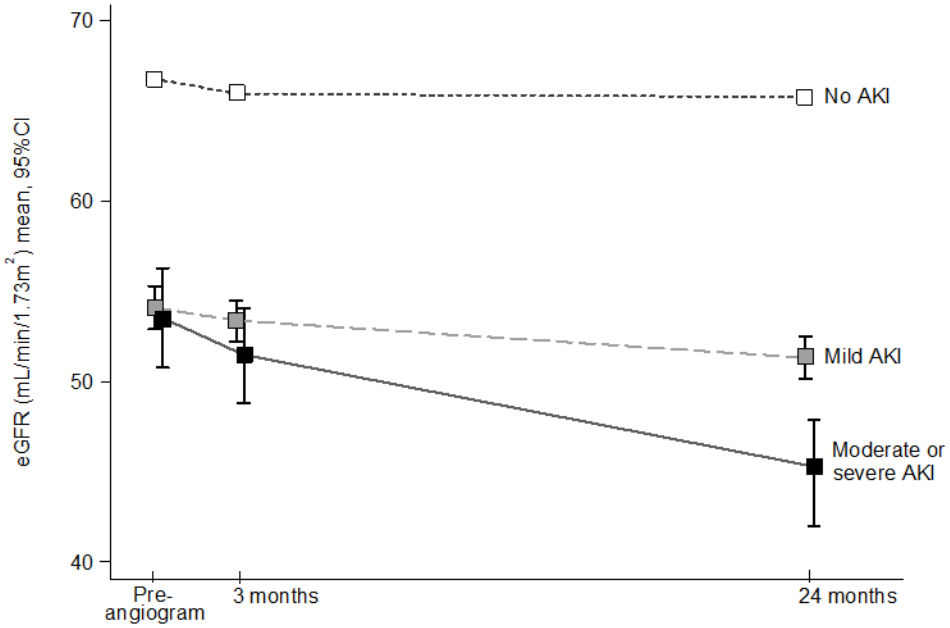
Abbreviations: AKI = Acute Kidney Injury, eGFR = estimated glomerular filtration rate

Figure 3.2 – Cohort formation.



Abbreviations: ESRD = End-Stage Renal Disease, CABG = Coronary Artery Bypass Graft, eGFR = estimated glomerular filtration rate

Figure 3.3 – Kidney function following coronary angiography among patients with post-angiography eGFR < 90 mL/min/1.73m^2, according to Acute Kidney Injury status



Abbreviations: eGFR = estimated Glomerular Filtration Rate, AKI = Acute Kidney Injury

Chapter Four: Associations between Acute Kidney Injury, Cardiovascular Events and Renal Outcomes after Coronary Angiography

4.1 Abstract

Background: Acute kidney injury (AKI) is associated with early mortality following percutaneous coronary revascularization procedures, but its prognostic relevance to long-term clinical outcomes remains controversial.

Methods and Results: We conducted a retrospective study of 14,782 adults who received coronary angiography in the province of Alberta, Canada between 2004 and 2006. AKI was identified based on changes in serum creatinine concentration within 7 days of the procedure according to AKI Network criteria. The associations between AKI and long-term outcomes including mortality, end-stage renal disease, and cardiovascular and renal hospitalizations were studied using Cox regression of multiple failure times. The adjusted risk of death increased with increasing severity of AKI: compared to no AKI, the adjusted hazard ratio (HR) for death was 2.00 (95% confidence interval [CI], 1.69 to 2.36), with stage 1 AKI, and 3.72 (95% CI, 2.92 to 4.76) with stage 2 or 3 AKI. The adjusted risk of end-stage renal disease requiring renal replacement therapy also increased according to the severity of AKI (HR 4.15 [95% CI, 2.32 to 7.42], and 11.74 [95% CI, 6.38 to 21.59], respectively), as did the risks of subsequent hospitalizations for heart failure and acute renal failure.

Conclusions: These findings inform the controversy surrounding AKI after angiography, demonstrating that it is a significant risk factor for long-term mortality, end-stage renal disease, and hospitalization for cardiovascular and renal events following coronary angiography.

4.2 Introduction

Acute kidney injury (AKI) complicates 7 – 15% of percutaneous coronary procedures and is attributed largely to the nephrotoxic effects of iodinated radiocontrast media[21;24;25]. Although severe AKI that requires acute dialysis is a rare event in this setting[264], lesser degrees of AKI (represented by small, usually reversible changes in serum creatinine concentration) have been associated with adverse in-hospital outcomes (including myocardial infarction and target vessel re-occlusion)[29;34], prolonged hospital stay[31;35], and early mortality[28;95].

Despite these observations, the true long-term clinical consequences of AKI following coronary angiography have remained controversial in light of observations that death following AKI is often complicated by other acute conditions not mediated by AKI, including cardiogenic shock, sepsis, respiratory failure, and bleeding[33;34]. Conversely, emerging associations between kidney function and cardiovascular disease suggest it is plausible that kidney injury may contribute to cardiovascular morbidity and mortality in addition to kidney failure following coronary angiography[29;33;41]. While it is known that patients who develop AKI are at increased risk of death following coronary angiography[27;34], little is known about the associations between AKI and specific cardiovascular and renal events. These associations are particularly relevant since pre-existing kidney disease is common in patients with cardiovascular disease as well as among patients who develop AKI[71;143], and because subsequent hospitalizations for cardiovascular events and kidney failure lead to adverse health consequences and high costs.

The purpose of this study was to examine the associations between AKI and long-term clinical outcomes (including death, progression to ESRD, and hospitalization for cardiovascular and renal events) following coronary angiography. We hypothesized that AKI would be an independent predictor of these outcomes following hospital discharge after adjustment for important cardiovascular and renal prognostic variables including anatomical location of coronary disease, ejection fraction, baseline glomerular filtration rate and proteinuria. Furthermore, we hypothesized that these associations would vary with the severity of AKI in a manner dependent on the outcome of interest.

4.3 Methods

4.3.1 Study population

The study cohort was derived retrospectively from the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH). APPROACH prospectively collects data on demographic and clinical characteristics on all patients undergoing coronary angiography in the province of Alberta, Canada[68]. Coronary angiography is performed using non-ionic iodinated radiocontrast agents with the choice of low- or iso-osmolar radiocontrast agents and use of prophylaxis strategies including N-acetylcysteine and intravenous fluid made at the discretion of treating physicians.

The cohort consisted of all Alberta residents, $\geq$ 18 years of age, undergoing coronary angiography from 1 January 2004 to 31 December 2006. Eligible participants required at least one outpatient serum creatinine measurement within a 6 month period prior to

coronary angiography, and a subsequent measurement (either inpatient or outpatient) within 7 days following the angiogram. Patients with a renal transplant or who were receiving dialysis prior to coronary angiography were excluded based on the Northern and Southern Alberta Renal Program registries[117] or by a period of continuous physician billing claims for dialysis[118].

4.3.2 Measurement of kidney function

All serum creatinine measurements made in Alberta were obtained from the Alberta Kidney Disease Network repository of laboratory data[69]. Pre-angiography kidney function was determined using the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation[120] to estimate glomerular filtration rate (eGFR)[69]. AKI was defined based on the change in serum creatinine concentration from the pre-angiogram level to the peak level observed within 7 days following the coronary angiogram or prior to CABG surgery if the later was performed within 7 days of angiography. The change in creatinine concentration was calculated using the most recent measurement prior to the angiogram as the baseline, and categorized according to the Acute Kidney Injury Network criteria (AKI stage 1 ≥0.3 mg/dl [26 μmol/L] absolute or 1.5-2.0 fold relative increase in serum creatinine; AKI stage 2 >2-3 fold increase in serum creatinine; AKI stage 3 > 3 fold increase in serum creatinine or serum creatinine ≥4.0 mg/dl [354 μmol/L)]with an acute rise of >0.5 mg/dL [44 μmol/L])[12]. Sensitivity analysis was also performed restricting the analysis to patients with a baseline creatinine measurement within 2 days prior to the angiogram.

4.3.3 Measurement of covariates

Age, sex, comorbidity, coronary anatomy (based on Duke myocardial jeopardy score[144]), left ventricular systolic ejection fraction, and subsequent receipt of coronary revascularization procedures (none, percutaneous coronary intervention [PCI], or coronary artery bypass grafting [CABG]) were determined from the APPROACH database[68]. Provincial laboratory data were used to obtain all quantitative or semi-quantitative outpatient urinary protein or albumin measurements collected within 6 months prior to angiography[69]. Urine protein was categorized as normal, microalbuminuria / proteinuria, or unmeasured[123], based on the most recent pre-angiography urine specimen for patients with more than one result available.

4.3.4 Measurement of Outcomes

Participants were followed for a maximum of 39 months from the date of coronary angiography until death or the study end date (31 March, 2007). Study endpoints included death from any cause (as recorded by the Alberta Bureau of Vital Statistics which maintains records of deaths for all residents of the province of Alberta) and progression to ESRD (identified based on date of registration for chronic dialysis or renal transplantation within one of the Alberta renal programs)[117]. Participants were also followed-up from the date of hospital discharge until the next cardiovascular hospitalization (with a most responsible diagnosis of myocardial infarction, heart failure, or cerebrovascular accident), hospitalization with acute renal failure, and hospitalization for any other cause. Cause specific hospitalizations were identified from provincial

hospital discharge records using validated *ICD-9* and *-10* coding algorithms[136;145-147] (Table 4.1).

4.3.5 Statistical analysis

Differences in baseline characteristics according to AKI stage were compared using analysis of variance and Chi-squared tests for continuous and categorical variables, respectively. Cumulative incidence curves for mortality, ESRD, and first hospitalization for any cause were plotted according to AKI stage. Cox proportional hazards regression was used to model multiple failure times per subject (i.e., time to death, ESRD, hospitalization for myocardial infarction, hospitalization for heart failure, hospitalization for cerebrovascular accident, hospitalization for acute renal failure, and other hospitalizations) as a function of AKI stage, accounting for the correlation in the data using robust variance methods. A competing risk model for correlated unordered events of different type, stratified by outcome type, was fitted under the assumption that the exposure could be associated with repeated events in the same individual. In this model each outcome can occur once per patient, all patients are at risk for all outcomes, and when a patient experiences one outcome he or she remains at risk for all other outcomes, unless death occurs[148]. Participants were censored at the end of follow-up or death. The final model was built looking at single event models to identify stratum specific effects of exposure and covariates. Covariates considered for adjustment, included terms corresponding to the 18 baseline characteristics listed in Table 4.2. Stepwise elimination with backwards selection was used to select the most parsimonious set of predictive

variables. The proportional hazards assumption for the Cox model was tested and satisfied.

In sensitivity analyses we repeated models after excluding patients with missing data on proteinuria, severity of coronary artery disease, or left ventricular ejection fraction. All statistical analyses were conducted using STATA (version 11.0; STATA Corp., College Station, TX). The conjoint health research ethics board of the University of Calgary approved the study.

4.4 Results

4.4.1 Cohort formation and baseline characteristics

We identified 24,873 Alberta residents 18 years of age or older undergoing coronary angiography during the cohort entry period. We excluded 327 patients receiving renal replacement therapy prior to study entry, 1,105 without a creatinine measurement prior to coronary angiography, and 8,659 patients without a creatinine measurement in the 7 days following coronary angiography (Figure 4.1). Of the patients without a creatinine measurement within 7 days post-angiogram, 8,352 (96.4%) were discharged home on the day of the angiogram. The subsequent rates of death, progression to ESRD, and all cause hospitalization during long-term follow-up were 3.8%, 0.2%, and 45.9%, respectively, in this subgroup.

Of the 14,782 participants included in the final cohort, 1,099 (7.4%) experienced stage 1 AKI, and 321 (2.2%) stage 2 or 3 AKI. These participants were older, had lower pre-

angiography eGFR, proteinuria, and were more likely to have certain comorbidities (including diabetes mellitus, hypertension, and heart failure), lower left ventricular ejection fraction and more severe coronary artery disease (Table 4.2). In addition, participants experiencing AKI were less likely to receive PCI, and more likely to receive CABG as a subsequent revascularization procedure.

4.4.2 Unadjusted Rates of Clinical Outcomes by Severity of AKI

Over a median follow-up after discharge of 19.7 months (interquartile range 10.8 – 28.8 months), 1,103 (7.5%) patients died, 93 (0.6%) progressed to ESRD requiring renal replacement therapy, and 6,230 (42.1%) were hospitalized. The unadjusted cumulative incidence of death, ESRD, and all cause hospitalization according to stage of AKI are shown in Figure 4.2. The incidence of mortality and ESRD both increased in a graded manner with greater severity of AKI (p-trend <0.001 for both outcomes). The cumulative incidence of all cause hospitalization exceeded 40% regardless of AKI status, and did not increase in a graded manner with greater severity of AKI (p-trend 0.137)

4.4.3 Adjusted Rates of Clinical Outcomes by Severity of AKI

In the adjusted models, AKI remained associated with increases in the risks of death, progression to ESRD, as well as other cardiovascular and renal specific hospitalizations (Figure 4.3). Significant differences were present in the strength of associations between AKI stage and the outcome type (p-value for interaction by strata < 0.001). Compared to those without AKI, the fully adjusted risk of mortality increased 2-fold in those with AKI stage 1, and more than 3-fold in those with AKI stage 2 or 3. The adjusted risk of ESRD

was most substantially increased in those with stage 2 or 3 AKI, in whom a more than 11-fold increase in risk was observed. The adjusted risk of hospitalization for myocardial infarction was 47% greater among those with stage1 AKI although this risk was not significantly elevated in those with stage 2 or 3 AKI. The adjusted risk of hospitalization for heart failure increased by 48%in those with AKI stage 1, and by more than 2-fold in those with AKI stage 2 or 3. Hospitalization for cerebrovascular accident was uncommon and was not significantly associated with AKI in adjusted models. Subsequent hospitalizations with AKI were more than 2- and 3-fold higher in those with stage 1 and stage 2 or 3 AKI, respectively. No significant associations were observed between AKI and the adjusted risk of hospitalization for other causes.

Results were similar when patients without measurements of proteinuria, severity of coronary artery disease, or left ventricular ejection fraction were excluded from the analysis, and when the analysis was restricted to patients with a baseline creatinine measurement within 2 days prior to the angiogram. Rates of adverse outcomes were increased in those with AKI for participants with Chronic Kidney Disease (CKD; pre-angiography eGFR < 60 mL/min/1.73m^2) or without CKD prior to coronary angiography (Table 4.3).

4.5 Discussion

In this population based cohort undergoing coronary angiography, the risks of death, progression to ESRD, and subsequent hospitalization for cardiovascular and renal events rose with increasing severity of AKI, although the gradient of risk across stages of AKI

differed among these events. Death was a common outcome and a graded increase in the risk of mortality was observed across the categories of AKI. The risk of subsequent hospitalizations for heart failure and acute renal failure also increased progressively with increasing severity of AKI, while the risk of progression to ESRD requiring renal replacement therapy was most substantial in those with the most severe episodes of AKI.

The association between even small changes in serum creatinine and adverse short –term clinical outcomes has been repeatedly documented[15;16;34]. Graded increases in mortality within 30 days of coronary angiography, and increased length of hospital admission have been shown to correlate with increases in the severity of AKI following coronary angiography[35]. Among patients receiving percutaneous coronary interventions, AKI has been shown to be associated with other early complications including myocardial infarction[29;34], target vessel re-occlusion[29], post-procedure bleeding complications[34], and the need for mechanical ventilation or circulatory support[31;34].

The effects of AKI following coronary angiography on long-term adverse cardiovascular and renal events are less clear. Most previous studies of contrast related AKI have identified events occurring during a short period of follow-up, have not included renal events as outcomes of interest, or were not able to account for important confounders relevant to the risk of future cardiovascular or renal events[130;149]. Other large cohorts of patients hospitalized with myocardial infarction (only a minority of whom received coronary procedures), have observed that during long-term follow-up, those with small increases in serum creatinine experienced increased rates of death (up to 19.4-27.5 deaths

per 100 patient years), comparable to those observed in our study[66;106]. Our findings also further extend knowledge about the prognostic implications of AKI following coronary angiography, including its graded associations with subsequent hospitalizations with heart failure and renal failure, and with risk of future progression to ESRD. Although the risk of myocardial infarction was higher in patients with mild but not severe episodes of AKI, differences in the presentation of acute coronary syndromes in patients with renal insufficiency[108] and competing risks for death may have contributed to this finding.

The associations between AKI and these long-term risks following AKI have several possible explanations. First, patients who develop AKI have a higher prevalence of comorbidities such as diabetes mellitus, heart failure, and chronic kidney disease, each of which may themselves increase the risk of heart failure, progression to kidney failure, and death[71;143]. However, the strength of the associations that remain after adjustment for important variables related to baseline kidney function and severity of cardiovascular disease suggests that confounding by these characteristics do not completely explain our findings, although we cannot rule out the possibility of residual confounding. Second, AKI may identify patients with impaired cardiac output or renal hemodynamic vulnerability who are at heightened long-term risks for decompensated heart function, loss of kidney function, and death. The long-term risks of adverse outcomes following AKI may be related to chronic effects on kidney function after an episode of AKI. Recent studies suggest that episodes of AKI contribute to persistent loss of kidney function[18;59], and faster subsequent rate of decline in kidney function[60;150] – processes which have been associated with future risks of episodes of heart failure[151] and

progression to ESRD[115]. Regardless of causality, the occurrence of AKI does appear to accurately identify a group of patients at higher risk for these adverse events, suggesting that targeting these patients for careful outpatient management has the potential to improve long-term outcomes.

These findings are important because there are a number of therapeutic interventions that have been shown to be of value in improving survival, slowing the progression towards ESRD, and preventing hospital admissions in general populations of patients with CKD[37] or with heart failure[152;153]. Early clinical follow-up, evaluation of volume status, use of diuretics, and inhibitors of the renin-angiotensin system have the potential to improve these outcomes following an episode of AKI; however, further research is needed to evaluate the role of these therapies specifically in survivors of AKI following coronary angiography.

There are several strengths to our study including a source population of all patients undergoing coronary angiography within a defined geographic region in which all residents had access to province-wide funded health care. Our cohort undergoing coronary angiography was well characterized, and included detailed information on important prognostic variables related to severity of cardiovascular disease and kidney disease prior to angiography. We were able to adjust for these important confounders as they related to each of the outcomes of interest in our modeling process.

Our study also has limitations. First, because this study was conducted as a historical cohort study using clinical data, participant selection was limited to patients with clinical concerns or illness that prompted follow-up creatinine measurement within 7 days. Since many patients who were discharged promptly and did not have a follow-up creatinine measurement were excluded, our results may overestimate the overall incidence of these events among all patients undergoing coronary angiography. However, the risks of clinical events in the excluded group without follow-up creatinine measurement were comparable to participants without AKI, suggesting that exclusion of these patients is unlikely to have biased estimates of risk relative to the reference group with serum creatinine measurements available but no AKI. Second, episodes of AKI and their severity may have been misclassified due to our dependence on existing creatinine measurements captured following coronary angiography. However, our approach to identification of AKI is most vulnerable to missing episodes of mild AKI or underestimating the severity of AKI in those who developed it. If such misclassification occurred, we anticipate this would have attenuated the relative risk of outcomes associated with the moderate or severe forms of AKI. Finally, despite our attempts to control for important confounding variables, residual confounding due to unmeasured variables (volume and type of contrast received, use of prophylactic measures, exposure to other nephrotoxins, and the contribution of atheroembolism) or differences in the severity of CKD or other comorbidities between groups remains possible. Observational studies of this nature cannot prove that AKI plays a causal role in these outcomes, or that prevention of AKI would improve these long-term outcomes. These results should not be interpreted as evidence that patients at risk for AKI should avoid diagnostic and

interventional coronary procedures, as several studies have documented that patients with kidney disease who do not receive these procedures have poorer outcomes[10;154]. However, our findings suggest that long-term mortality, ESRD, and cardiovascular and renal hospitalizations would be important outcomes to examine in future randomized trials of interventions targeting post-angiography AKI.

In conclusion, graded increases in the severity of AKI are associated with variation in risks of long-term mortality, progression to ESRD, and hospitalization for cardiovascular and renal events. The presence and severity of AKI following coronary angiography could be used to help identify high risk patients and guide further management. Further research focusing on interventions to prevent AKI following coronary angiography should assess the effects on these important clinical outcomes. Strategies to reduce cardiovascular risk and slow the progression of CKD require further study in survivors of radiocontrast-associated AKI.

Table 4.1 - Identification of study outcomes

Outcome	Criteria
Mortality	Alberta Vital Statistics record
End-stage renal disease	Registry for dialysis or kidney transplantation in Northern or Southern Alberta Renal Program
Hospitalization for myocardial infarction	ICD-9: 410 ICD-10: I21, I22
Hospitalization for heart failure	ICD-9: 428 ICD-10: I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5, I42.6, I42.7, I42.8, I42.9, I43, I50, P29.0
Hospitalization for cerebrovascular accident	ICD-9: 362.3, 430, 431, 433, 434, 435, 436 ICD-10: H341,I60, I61, I63, I64, G45
Hospitalization for acute renal failure	ICD-9: 584.5, 584.6, 585.7, 584.8, 584.9 ICD-10: N17.0, N17.1, N17.2, N17.8, N17.9

Abbreviations: ICD = International Classification of Diseases

Table 4.2 - Characteristics of patients undergoing coronary angiography, according to acute kidney injury status.

	Acute Kidney Injury±			
	No AKI (n=13,362)	**AKI Stage 1 (n=1,099)**	**AKI Stage 2/3 (n=321)**	**p-value †**
Age, yr, mean (SD)	62.6 (12.4)	68.0 (12.1)	67.4 (12.7)	<0.001
Sex, male, No. (%)	9,564 (71.6)	779 (70.9)	217 (67.6)	0.27
Pre-angiography serum creatinine,mg/dl, Mean (SD)	1.0 (0.3)	1.2 (0.5)	1.6 (1.3)	<0.001
Pre-angiography eGFR, mL/min/1.73m^2, Mean (SD)	75.3 (21.0)	66.6 (12.6)	58.5 (31.4)	<0.001
Pre-angiography eGFR, Categories, No. (%):				
≥ 60 mL/min/1.73m^2	10,467 (78.3)	629 (57.2)	143 (44.5)	<0.001
45 – 59 mL/min/1.73m^2	2,104 (15.7)	242 (22.0)	71 (22.1)	
30 – 44 mL/min/1.73m^2	634 (4.7)	172 (15.7)	46 (14.3)	
< 30 , mL/min/1.73m^2	157 (1.2)	56 (5.1)	61 (19.0)	
Proteinuria, No (%):				
Absent	8,156 (61.0)	617 (56.1)	157 (48.9)	<0.001
Microalbuminuria / proteinuria	1,512 (11.3)	242 (22.0)	110 (34.3)	
Unmeasured	3,694 (27.6)	240 (21.8)	54 (16.8)	
Comorbidities, No (%):				
Diabetes mellitus	3,283 (24.6)	365 (33.2)	134 (41.7)	<0.001
Hypertension	8,682 (65.0)	798 (72.6)	230 (71.6)	0.020
Hyperlipidemia	10,096 (75.6)	796 (72.4)	206 (64.2)	<0.001
Heart failure	1,799 (13.5)	312 (28.4)	142 (44.2)	<0.001
Cerebrovascular disease	920 (6.9)	126 (11.5)	50 (15.6)	<0.001
Peripheral vascular disease	998 (7.5)	126 (11.5)	57 (17.8)	<0.001
Chronic pulmonary disease	2,126 (15.9)	268 (24.4)	83 (25.8)	<0.001
Liver disease	176 (1.3)	19 (1.7)	13 (4.0)	0.001
Malignancy	548 (4.1)	57 (5.2)	13 (4.0)	0.22
Current smoker	4,205 (31.5)	278 (25.3)	69 (21.5)	0.001

Acute coronary syndrome, No (%)	9,554 (71.5)	828 (75.3)	235 (73.2)	0.021
Coronary vascular disease, No (%):				
Normal	953 (7.1)	57 (5.2)	32 (10.0)	<0.001
Minimal (<50% stenosis)	1,223 (9.2)	64 (5.8)	19 (5.9)	
Low risk (1 or 2 vessel)	6,282 (47.0)	392 (35.7)	83 (25.8)	
High risk (3 vessel of proximal LAD)	3,844 (28.8)	405 (36.8)	119 (37.1)	
Left main	961 (7.2)	168 (15.3)	62 (19.3)	
Missing	99 (0.7)	13 (1.2)	6 (1.9)	
Left ventricular ejection fraction, No. (%):				
> 50 %	7,716 (57.7)	412 (37.5)	89 (27.7)	<0.001
35 – 50 %	2,816 (21.1)	268 (24.4)	73 (22.7)	
20 – 34 %	691 (5.2)	97 (8.8)	33 (10.3)	
< 20%	196 (1.5)	29 (2.6)	9 (2.8)	
Unmeasured	1,943 (14.5)	293 (26.7)	117 (36.4)	
Procedures, No (%):				
Only coronary angiography	3,909 (29.2)	310 (28.2)	121 (37.7)	0.003
Percutaneous coronary intervention	7,398 (55.4)	497 (45.2)	106 (33.0)	
Coronary artery bypass surgery	2,055 (15.4)	292 (26.6)	94 (60.4)	

† from ANOVA or Chi squared test

± Defined according to Acute Kidney Injury Network Criteria (AKI stage 1 ≥0.3 mg/dl [26.4 μmol/L] absolute or 1.5-2.0 fold relative increase in serum creatinine; AKI stage 2 >2-3 fold increase in serum creatinine; AKI stage 3 > 3 fold increase in serum creatinine or serum creatinine ≥4.0 mg/dl [354 μmol/L] with an acute rise of >0.5 mg/dL [44 μmol/L]).

Abbreviations: AKI = Acute Kidney Injury, SD = Standard Deviation, eGFR = estimated Glomerular Filtration Rate, LAD = Left Anterior Descending, N/A = Not Assessed

Table 4.3 – Rates of mortality, end-stage renal disease, and cardiovascular and renal hospitalizations stratified by acute kidney injury (AKI) status and pre-angiography eGFR.

	Rate (95% CI) per 100 person years	
	Pre-angiography eGFR ≥ 60 mL/min/1.73m^2	**Pre-angiography eGFR < 60 mL/min/1.73m^2**
Death		
No AKI	2.5 (2.3-2.8)	7.4 (6.6-8.2)
AKI Stage 1	8.5 (6.9-10.6)	19.2 (16.3-22.9)
AKI Stage 2/3	27.9 (21.0-37.2)	34.3 (27.3-43.2)
End-stage Renal Disease		
No AKI	0.2 (0.1-0.6)	0.5 (0.4-0.8)
AKI Stage 1	0.4 (0.2-1.1)	3.4 (0.4-0.8)
AKI Stage 2/3	0.6 (0.1-4.3)	22.0 (16.0-30.3)
Myocardial Infarction Hospitalization		
No AKI	2.0 (1.8-2.3)	2.8 (2.3-3.3)
AKI Stage 1	3.8 (2.7-5.2)	4.9 (3.4-7.0)
AKI Stage 2/3	1.2 (0.3-5.0)	5.7 (3.1-10.2)
Heart Failure Hospitalization		
No AKI	1.3 (1.1-1.5)	4.2 (3.6-4.8)
AKI Stage 1	2.9 (2.0-4.2)	10.0 (7.8-13.0)
AKI Stage 2/3	11.8 (7.3-19.0)	12.0 (7.9-13.0)
Cerebrovascular Accident Hospitalization		
No AKI	0.5 (0.4-0.6)	1.3 (1.0-1.6)
AKI Stage 1	0.9 (0.5-1.8)	0.9 (0.4-2.1)
AKI Stage 2/3	1.2 (0.3-4.9)	1.4 (0.5-4.5)
Acute Renal Failure Hospitalization		
No AKI	0.6 (0.5-0.7)	3.4 (3.0-4.0)
AKI Stage 1	2.4 (1.6-3.6)	9.9 (7.7-12.9)
AKI Stage 2/3	11.6 (7.2-18.6)	21.2 (1.5-3.0)
Other Hospitalization		
No AKI	27.7 (25.8-27.6)	36.6 (34.4-38.9)
AKI Stage 1	40.7 (35.7-46.4)	43.5 (36.9-51.3)
AKI Stage 2/3	35.6 (25.1-50.7)	25.6 (17.5-37.3)

AKI defined according to Acute Kidney Injury Network Criteria (AKI stage 1 ≥0.3 mg/dl [26.4 μmol/L] absolute or 1.5-2.0 fold relative increase in serum creatinine; AKI stage 2 >2-3 fold increase in serum creatinine; AKI stage 3 > 3 fold increase in serum creatinine or serum creatinine ≥4.0 mg/dl [354 μmol/L] with an acute rise of >0.5 mg/dL [44 μmol/L])

Abbreviations: AKI = Acute Kidney Injury SD = Standard Deviation, eGFR = estimated Glomerular Filtration Rate

Figure 4.1 – Cohort Formation

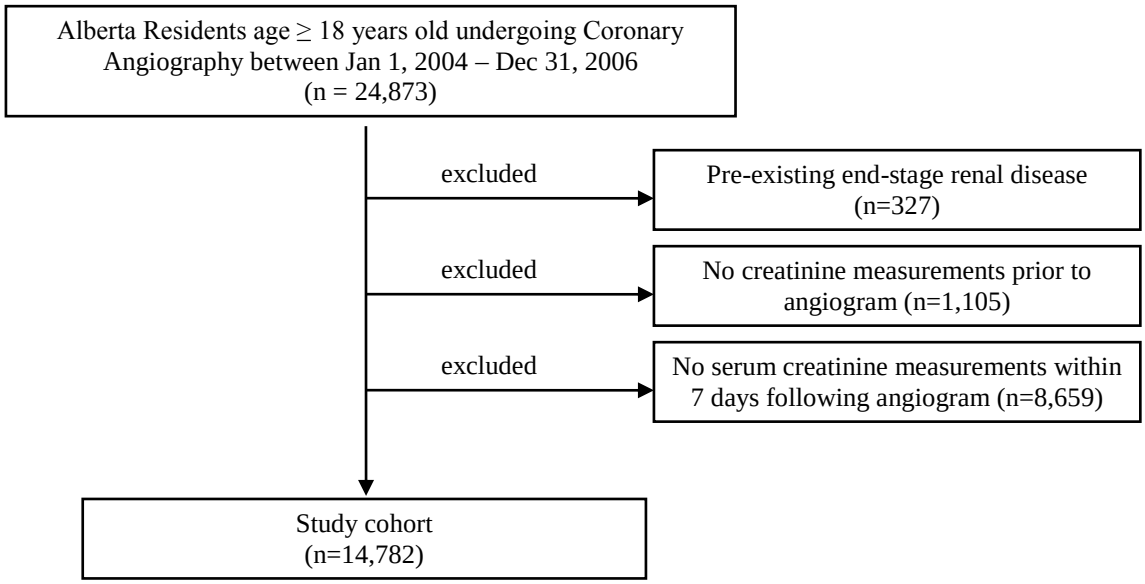
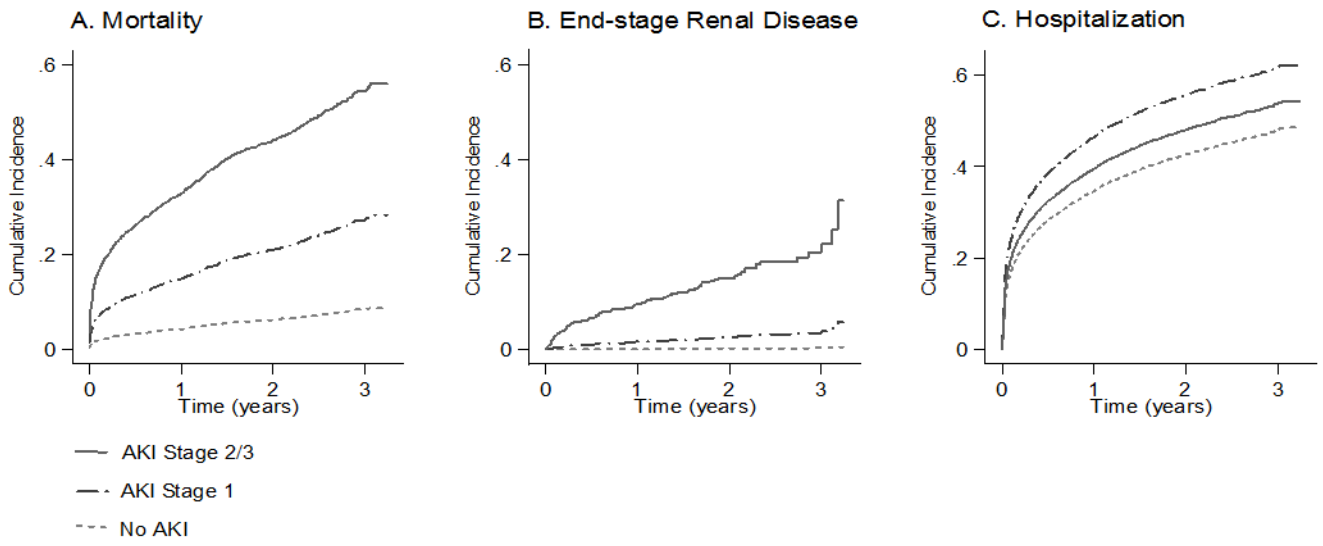


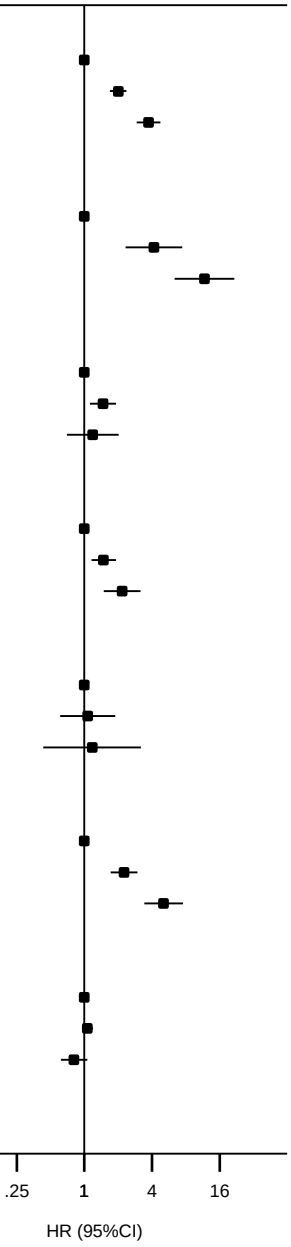
Figure 4.2 - Cumulative incidence of (A) Mortality, (B) End-stage Renal Disease, and (C) Hospitalization for all causes, according to stage of acute kidney injury (AKI).



Acute Kidney Injury Network Criteria (AKI stage 1 ≥0.3 mg/dl absolute or 1.5-2.0 fold relative increase in creatinine; AKI stage 2 >2-3 fold increase in creatinine; AKI stage 3 > 3 fold increase in creatinine or ≥4.0 mg/dl with rise >0.5 mg/dL)

Figure 4.3 - Rates and adjusted hazard ratios for all-cause mortality, end-stage renal disease, and hospitalization for cardiovascular, renal, and other events, according to stage of acute kidney injury (AKI).

Outcome AKI stage	Events / person--years	Rate (95% CI) (per 100 person-years)	HR (95% CI)
Mortality			
No AKI	777/21888	3.5 (3.3-3.8)	1 [Reference]
AKI Stage 1	206/1625	12.7 (11.0-14.5)	2.00 (1.69-2.36)
AKI Stage 2/3	120/381	31.5 (26.3-37.7)	3.72 (2.92-4.76)
End-stage Renal Disease			
no AKI	29/21864	0.1 (0.1-0.2)	1 [Reference]
AKI Stage 1	25/1610	1.6 (1.0-2.3)	4.15 (92.32-7.42)
AKI Stage 2/3	39/339	11.5 (8.4-15.7)	11.74 (6.38-21.59)
Myocardial Infarction Hospitalization			
No AKI	468/21366	2.2 (2.0-2.4)	1 [Reference]
AKI Stage 1	65/1540	4.2 (3.3-5.4)	1.47 (1.12-1.91)
AKI Stage 2/3	13/355	3.6 (2.1-6.3)	1.19 (0.70-2.02)
Heart Failure Hospitalization			
No AKI	407/21476	1.9 (1.7-2.1)	1 [Reference]
AKI Stage 1	87/1538	5.7 (4.6-7.0)	1.48 (1.16-1.91)
AKI Stage 2/3	39/327	11.9 (8.7-16.3)	2.17 (1.49-3.15)
Cerebrovascular Accident Hospitalization			
No AKI	145/21825	0.7 (0.6-0.8)	1 [Reference]
AKI Stage 1	15/1604	0.9 (0.6-1.6)	1.07 (0.61-1.89)
AKI Stage 2/3	5/370	1.4 (0.6-3.2)	1.18 (0.43-3.19)
Acute Renal Failure Hospitalization			
No AKI	259/21741	1.2 (1.0-1.3)	1 [Reference]
AKI Stage 1	81/1547	5.2 (4.2-6.5)	2.25 (1.71-2.96)
AKI Stage 2/3	47/288	16.3 (12.2-21.7)	5.08 (3.41-7.58)
Other Hospitalization			
No AKI	4176/14642	28.5 (27.7-29.4)	1 [Reference]
AKI Stage 1	365/874	41.7 (37.7-46.2)	1.06 (0.95-1.19)
AKI Stage 2/3	58/192	30.1 (23.3-39.0)	0.81 (0.62-1.06)



AKI defined according to Acute Kidney Injury Network Criteria (AKI stage 1 ≥0.3 mg/dl [26.4 μmol/L] absolute or 1.5-2.0 fold relative increase in creatinine; AKI stage 2

>2-3 fold increase in creatinine; AKI stage 3 > 3 fold increase in creatinine or ≥4.0 mg/dl [354 mmol/L] with rise >0.5 mg/dL [44 μmol/L])

Covariates (by stratum) retained in the final model were age (all strata), sex (all strata), diabetes mellitus (all strata), heart failure (all strata), cerebrovascular disease (mortality, MI, CVA, other hospitalization strata), peripheral vascular disease (mortality, MI strata), chronic pulmonary disease (mortality, other hospitalization strata), liver disease (mortality, other hospitalization strata), malignancy (mortality, other hospitalization strata), current smoking (mortality, MI, CVA, other hospitalization strata), acute coronary syndrome(mortality, MI, other hospitalization strata) baseline estimated Glomerular Filtration Rate (all strata), microalbuminuria/proteinuria (all strata),coronary anatomy based on Duke myocardial jeopardy score (mortality, MI, CVA strata), left ventricular ejection fraction (mortality, heart failure, ESRD, ARF, and other hospitalization strata), and coronary revascularization (all strata).

Abbreviations: HR = Hazard Ratio; CI = Confidence Interval, AKI = Acute Kidney Injury, MI = Myocardial Infarction, CVA = Cerebrovascular Accident, ESRD = End-stage Renal Disease, ARF = Acute Renal Failure

Chapter Five: Renal Outcomes Related to Early Invasive versus Conservative Management of Acute Coronary Syndrome

5.1 Abstract

Background - Acute kidney injury is a predictable complication following coronary angiography associated with adverse short and long-term outcomes. The risk of acute kidney injury and other adverse renal events associated with invasive versus conservative management of acute coronary syndrome is unclear. We performed a retrospective cohort study to examine the association of early invasive management with acute kidney injury, dialysis, end-stage renal disease, and survival.

Methods Alberta residents aged 18 years or older with a primary admission diagnosis of non-ST elevation acute coronary syndrome from six acute care hospitals in Alberta, Canada between 1 January 2004 and 31 October 2009 were studied. Patients were classified as receiving early invasive (coronary angiography performed within 2 days of hospital admission) versus conservative management, and followed to determine the risks of acute kidney injury (>0.3 mg/dl or 50% increase in serum creatinine concentration during hospitalization), acute kidney injury requiring dialysis, end-stage renal disease, and all-cause mortality.

Results Of 10,538 included patients, 4,281 (40.6%) received early invasive management. After propensity score methods were used to assemble a matched cohort of conservative management patients with characteristics similar to those who received early invasive therapy (n=7,430), early invasive management was associated with an increased risk of acute kidney injury (8.8% versus 5.6%, risk ratio (RR) 1.52, 95% CI 1.29 to 1.80; P<0.001). However, no significant differences were observed between the matched groups in the risks of acute kidney injury requiring dialysis during hospitalization (0.3%

vs 0.2%, RR 1.33 [0.56 – 3.16], p=0.514) or end-stage renal disease (hazard ratio [HR] 0.81 [0.68 – 0.96], p=0.019). Early invasive management was associated with improved long-term survival (HR 0.71 [0.68 – 0.96], p=0.019).

Conclusions Early invasive management is associated with a modest increase in risk of acute kidney injury but not dialysis or end-stage renal disease in patients with acute coronary syndrome. These findings suggest that the risk of acute kidney injury should not preclude early invasive management of acute coronary syndromes.

5.2 Introduction

In North America, approximately 40% of patients with acute coronary syndromes (ACS) receive early invasive therapies including coronary angiography and percutaneous coronary intervention (PCI) within 48 hours of hospital admission[8]. Early invasive management reduces recurrent angina, re-hospitalization and myocardial infarction, and improves long-term survival in high risk patients compared to a conservative approach (reserving invasive procedures for patients with signs of ongoing ischemia despite medical management) for non-ST elevation acute coronary syndromes[6;155;156]. Accordingly, current American College of Cardiology / American Heart Association guidelines recommend early invasive therapy for high risk patients with non-ST elevation acute coronary syndromes[157], though observational studies suggest that not all eligible patients receive these interventions[8;10;158].

Acute kidney injury (AKI) complicates up to 30-50% of coronary interventions in high risk subgroups[28;32], and is associated with adverse outcomes including prolonged hospitalization, recurrent cardiovascular events, and mortality[27;34;35]. Fear of precipitating AKI due to radiocontrast nephropathy may contribute to under use of invasive therapy in high risk patients (including those with older age and renal insufficiency)[8;10;158], despite their higher risk of adverse outcomes and potential for greater absolute benefit[9]. While several studies have reported on the risks of AKI in patients receiving invasive procedures[27;29;34;71], little is known about the risks of AKI in patients with ACS who are treated with a conservative approach. Furthermore, the risks

of acute or chronic dialysis associated with an invasive approach (as compared to conservative management) remain unclear.

Given these knowledge gaps, we did a retrospective cohort study of patients receiving early invasive versus conservative management of ACS. We aimed to compare the risks of AKI, dialysis, end-stage renal disease (ESRD), and survival between early invasive and conservative treatment strategies.

5.3 Methods

5.3.1 Study Cohort

We did a retrospective cohort study linking data from a clinical registry of patients hospitalized for ACS with administrative healthcare and laboratory data in Alberta, Canada. The study cohort was derived from the Heart Alert Registry of the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH)[68]. Heart Alert prospectively collects data on demographics, clinical characteristics, management strategies, and outcomes for patients admitted with a primary diagnosis of ACS to any of six acute-care hospitals in Southern Alberta, Canada. Cardiac catheterization was performed at only one of these hospitals during the study period.

The cohort consisted of all Alberta residents, ≥ 18 years of age, admitted to a Heart Alert registry hospital with Non-ST segment ACS between 1 January 2004 and 31 October 2009. We excluded patients admitted with ST elevation myocardial infarction, as regional practices at the time of this study included emergent primary angioplasty as the

principal treatment approach. Eligible participants required at least one inpatient serum creatinine measurement within the first 2 days of hospitalization to establish admission kidney function. Patients receiving chronic dialysis prior to coronary angiography were excluded[117].

5.3.2 Measurement of Exposure

Participants were defined as receiving early invasive management if they received coronary angiography (with or without PCI) within 2 days of hospital admission; all other participants were classified as receiving conservative management. We also performed sensitivity analyses in which patients who received any invasive therapy during hospital admission were distinguished from those who received medical therapy only during the hospitalization.

5.3.3 Measurement of Covariates

Information on demographic characteristics, comorbidities, vital signs, electrocardiogram, and cardiac enzymes at admission were determined from the Heart Alert registry of the APPROACH database. Missing data on medical comorbidities was enhanced by linking to provincial health care administrative care records as previously described[68;159;160]. Hypotension was defined as a presenting systolic blood pressure < 90 mmHg, and tachycardia as a presenting heart rate > 100 beats per minute. Cardiac enzymes were considered elevated if the concentration of troponin T or I or CK-MB on

the day of admission was above the reference range. Subsequent use and timing of coronary angiography, PCI, or CABG during the index hospitalization was also determined from the Heart Alert registry. Information on estimated glomerular filtration rate (eGFR), albuminuria, and hemoglobin concentration was obtained from the Alberta Kidney Disease Network (AKDN) repository of laboratory data[69]. Admission eGFR was determined using the first serum creatinine measurement obtained in hospital and calculated using the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation[121]. Albuminuria was defined by a semi-quantitative urine dipstick measurement $\geq$ 1+ or urine albumin-to-creatinine ratio > 3mg/dl within 6 months prior to admission[69]. Anemia was defined as a haemoglobin concentration < 13.0 g/dL for men, or < 12.0 g/dL for women at the time of admission[161]. Presentation to a catheterization facility was defined by initial admission to the hospital with facilities for cardiac catheterization.

5.3.4 Measurement of Outcomes

Short-term outcomes of interest during the index hospitalization were AKI, AKI treated with dialysis, and all-cause mortality. AKI was defined according to the AKI Network criteria based on a > 50% or 0.3 mg/dL (26.4 μmol/L) increase in serum creatinine concentration using the value obtained at the time of admission as the baseline measurement[12]. Acute kidney injury requiring dialysis was identified using a validated and highly accurate administrative data coding approach[136]. Long-term outcomes of interest were progression to ESRD (defined as registration for chronic dialysis or renal transplantation within one of the Alberta renal programs[117]), and all-cause mortality (determined from the Heart Alert registry by linkage to provincial vital statistics records) with follow-up until 31, December, 2009.

5.3.5 Statistical Analyses

Differences in patient characteristics according to treatment strategy for the entire cohort were compared using t-tests and Chi-squared tests for continuous and categorical variables, respectively. We used a propensity score approach to account for differences in measured admission characteristics between the two treatment groups. We developed a non-parsimonious multivariable logistic regression model to estimate the odds of receiving early invasive management. Covariate included in the model were age, sex, coronary risk factors (diabetes mellitus, hypertension, hyperlipidemia, cigarette smoking, family history of coronary artery disease), additional comorbidities (prior myocardial infarction, prior PCI, prior CABG, heart failure, peripheral vascular disease,

cerebrovascular disease), Charlson comorbidity score, admission eGFR, albuminuria, anemia, electrocardiographic evidence of ischemia (ST segment deviation), elevated cardiac enzymes (CK-MB, Troponin T or I), hypotension, tachycardia, and initial presentation to a hospital with a cardiac catheterization facility.

Initially we performed analyses within the entire cohort, stratifying participants across quintiles of the propensity score to control for differences in measured admission characteristics between treatment groups. The relative risks of AKI and in-hospital mortality were compared between participants who received early invasive therapy and those who received conservative therapy within each quintile of the propensity score using generalized linear models. For our primary analysis, we matched patients who received early invasive therapy to those who received conservative therapy on the basis of their propensity scores[162]. We used 1-to-1 matching without replacement with a caliper width of 0.02 of the log odds of the propensity score. We compared the balance in covariates before and after matching using standardized differences[163]. Continuous and categorical variables in the matched pairs were compared using statistical methods for paired data. The relative risks of short-term outcomes including AKI, AKI requiring dialysis, and in-hospital mortality in participants who received early invasive versus conservative therapy was compared using generalized estimating equations. Long-term outcomes including ESRD and survival were compared using Cox proportional hazards models accounting for frailty between matched pairs.

We also conducted a number of sensitivity analyses. First, we examined the effect of invasive versus conservative therapy extending the time period for receipt of the invasive procedure over the entire hospitalization, to determine if the results varied when patients who received invasive management (at any time during hospitalization) were matched with patients who received medical management only. Second, we excluded patients who died within the first 2 days of hospitalization to ensure that early mortality and survival bias did not influence our findings. Third, we excluded patients who were transferred to the hospital with catheterization facilities within 5 days of admission, to ensure delays in invasive management for logistical reasons did not influence our findings. Finally, we excluded patients who received CABG during the index hospitalization to explore whether a difference in utilization of surgical procedures, rather than diagnostic or angiographic procedures, explained our findings. All statistical analyses were conducted using STATA (version 11.0; STATA Corp., College Station, TX). The conjoint health research ethics board of the University of Calgary approved the study.

5.4 Results

A total of 10,697 Alberta residents > 18 years of age with an admission diagnosis of non-ST segment elevation ACS were eligible for inclusion. We excluded 113 (1.0%) patients who were receiving dialysis at admission, and 46 (0.4%) individuals without a measure of kidney function following hospital admission. The entire study cohort included 10,538 participants, of whom 4,281 (40.6%) received early invasive therapy (coronary angiogram) within 2 days of hospital admission. Admission characteristics of patients

who received early invasive management differed from patients who received a conservative approach (Table 5.1). Patients who received early invasive management were more likely to be men with cardiovascular risk factors (hypertension, hyperlipidemia, history of smoking, and family history of coronary artery disease) and a prior history of PCI, while they were less likely to be older, with greater comorbidity, albuminuria, anemia, and have abnormal vital signs. The strongest predictors of early invasive therapy were ST segment deviation, and presentation to a hospital with cardiac catheterization facilities, while patients with prior CABG, heart failure, and low admission eGFR had the least propensity to receive early invasive management (Table 5.2).

5.4.1 Propensity adjusted outcomes in the entire cohort

Processes of care during hospitalization differed between the two treatment groups. A total of 2,881 (46.1%) of patients who initially received a conservative approach went on to receive a coronary angiogram during hospitalization, with a median time to angiography in this subgroup of 6 days (interquartile range 4 to 8 days). Patients who received early invasive management were more likely than patients who received conservative management to go on to receive PCI (56.9% vs 22.7%, $p<0.001$), or CABG (11.6% vs 4.1%, $p<0.001$) during the index hospitalization.

When stratified across quintiles of the propensity score for early invasive management, the risk of AKI during hospitalization was highest in the lowest propensity score quintile (lowest propensity for early angiography) and was greater for those who received early

invasive management in each quintile (Figure 5.3). The risk of death during hospitalization was also highest in the lowest quintile, and the largest differences in risk of in-hospital mortality between the early invasive and conservative approaches were seen at the lowest propensity score quintiles. Similar relationships between the risks of AKI and in-hospital mortality across propensity-score quintiles were observed when patients were grouped according to invasive management at any time during hospitalization versus medical management alone (Figure 5.4).

The propensity score adjusted risk of AKI for the entire cohort was higher in patients who received an early invasive approach (Risk ratio [RR] 1.24, 95% Confidence Interval [CI] 1.08 – 1.41, p=0.001). However, the propensity score adjusted risk of AKI requiring dialysis did not differ between the two treatment groups (0.3% vs 0.4%, RR 1.06 95% CI 0.52 – 2.16, p= 0.87), and the adjusted risk of in-hospital mortality was lower in the early invasive therapy group (1.4% vs 4.2%; RR 0.68, 95% CI 0.51 – 0.90, p=0.008). During long-term follow-up there was no significant difference in the propensity adjusted risk of ESRD (2.4 vs 6.6 events per 1000 patient years, HR 0.70 95% CI 0.45 – 1.11, p=0.13). The long-term risk of death was lower in patients who received early invasive management (5.5 vs 16.3 events per 1000 patient years; HR 0.68 95% CI 0.51 – 0.91, p=0.010).

5.4.2 Outcomes in Propensity Matched Pairs

Of those receiving the early invasive strategy, 3715 (50.1%) were matched on the basis of their propensity score to 3,715 (84.7%) patients who received conservative therapy. The

balance of admission characteristics between the two groups was improved after matching on the propensity score (Table 5.3) (Figure 5.1). The mean standardized difference between the two groups decreased from 16.5% (range 2.6% – 46.2%) before matching to 1.2% (range 0.1 – 5.5%) after matching. Among the matched patients, those who received an early invasive approach remained more likely to receive PCI, or CABG during the hospitalization (Table 5.4).

Within the matched cohort, the risk of AKI was higher among patients who had received early invasive management (8.8% vs 5.6%; RR 1.52, 95% CI 1.29 – 1.80, $p<0.001$) (Table 5.4). This corresponded to one additional episode of AKI for every 31 patients treated with an early invasive approach instead of a conservative approach. However, the risk of AKI requiring dialysis was not significantly different between the two approaches (0.3% vs 0.2%; RR 1.33, 95% CI 0.56 – 3.16, $p=0.51$), nor was the risk of in-hospital mortality (1.6% vs 1.7%; RR 0.90 95% CI 0.64 – 1.29, $p=0.59$). During long-term follow-up there was again no significant difference in risk of ESRD (0.7% vs 1.0%; RR 0.71 95% CI 0.43 – 1.17, $p=0.12$), while the long-term adjusted risk of death was lower in matched patients who received early invasive management (5.9% vs 7.3%; RR 0.81 95% CI 0.68 – 0.96, $p=0.019$).

Of patients who received invasive management at any time during hospitalization, 2938 (27.9%) were matched by propensity score to 2,938 (47.0%) patients who received medical management only (Figure 5.2). Compared to patients who received medical therapy alone, matched patients who received invasive management were at similar risk

of AKI (10.5% vs 9.2%; RR 1.14, 95% CI 0.98 – 1.32, p=0.098), and AKI requiring dialysis (0.5% vs 0.4%; RR 1.25, 95% CI 0.58 – 2.67, p=0.56) during the index hospitalization. However, patients who received an invasive procedure at any time during hospitalization were at lower risk of in-hospital and long-term mortality than those managed medically (Table 5.5).

In sensitivity analyses, results were consistent with the primary analysis when we excluded patients who died within the first 2 days of hospitalization or when we excluded patients transferred from a hospital without cardiac catheterization facilities. When patients who died within the first 2 days of admission were excluded, matched patients who received early invasive management remained at higher risk of AKI (8.7% vs 5.8%; RR 1.51, 95% CI 1.28 – 1.78, p<0.001) but not in-hospital mortality (1.4% vs 1.6%; RR 0.90, 95% CI 0.63 – 1.29, p<0.071) or AKI requiring dialysis (0.3% vs 0.2%, RR 1.33, 95% CI 0.56 – 3.17, p=0.51). Results were similar when patients who received CABG during the index hospitalization were excluded, with early invasive therapy associated with a higher risk of AKI (7.0% vs 5.6%; RR 1.25, 95% CI 1.04 – 1.50, p=0.016) but not in-hospital mortality (1.5% vs 2.7%; RR 0.68, 95% CI 0.44 – 1.03, p<0.071) or AKI requiring dialysis (0.1% vs 0.2%, RR 0.36, 95% CI 0.10 – 1.34, p=0.127) compared with conservative therapy. The relative risks of AKI and mortality during hospitalization associated with early invasive therapy were not associated with age (less than versus greater than 65 years), diabetes mellitus, heart failure, admission eGFR (less than versus greater than 60 mL/min/1.73m^2), or comorbidity (Charlson comorbidity score less than versus greater than 2) (all p-interaction >0.10).

5.5 Discussion

In this retrospective cohort study, patients who received early invasive management for non-ST segment elevation ACS were more likely to develop AKI during hospitalization. Despite this finding, early invasive therapy was not associated with an increase in short term risk of AKI requiring dialysis, or long-term risk of ESRD, and, conversely, was associated with better long-term survival. Compared to medical management alone, the use of invasive procedures at any time during hospitalization did not increase the risk of AKI, AKI requiring dialysis, or ESRD, and was also associated with improved survival. These results suggest that the short term risks to renal function associated with invasive coronary procedures should not act as a deterrent to their use.

There is limited data on the risk of adverse renal events from randomized trials of early invasive versus conservative treatment for ACS, in part due to the exclusion of patients with moderate to severe renal insufficiency from trials. Among patients with baseline serum creatinine < 150 μmol/L enrolled in the FRISC trial, eGFR declined similarly in the early invasive and conservative treatment arms; however, the incidence of AKI, acute dialysis, and ESRD was not reported[164]. Several previous observational studies have demonstrated a high incidence of AKI following coronary angiography and PCI[28;32], and strong associations between AKI and death, major adverse cardiovascular events, and kidney failure requiring dialysis in this setting[27;34;35;71]. Although other studies have examined the links between AKI and mortality and ESRD in patients hospitalized with

myocardial infarction treated with either invasive or medical management[66;106], these studies have not compared renal outcomes on the basis of treatment strategies.

Our findings show that AKI is common in patients with ACS – whether they receive early invasive management or conservative management (without coronary angiography, PCI, or CABG). Importantly, despite the modestly higher risk of in-hospital AKI associated with early invasive management, this strategy is not associated with higher risks of more clinically relevant renal outcomes (acute or chronic dialysis). Given that early invasive management improves long-term survival[6;156], our results suggest that restricting or delaying access to invasive coronary procedures is unlikely to prevent clinically relevant AKI, and may deny patients important benefits.

There are several potential mechanisms for the increased risk of AKI associated with early invasive management. Patients who received early invasive management were more likely to receive coronary angiography, and PCI (placing them at higher risk of radio-contrast associated AKI) as well as CABG surgery (placing them at risk for perioperative AKI). However, the magnitude of the increased risk associated with invasive management strategies was small, suggesting that other characteristics such as age, comorbidity, pre-existing renal insufficiency, medication use (especially diuretics, beta-blockers, or inhibitors of the renin angiotensin system) or hemodynamic instability likely contribute to the risk of ACS-related AKI. Furthermore, patients with the lowest propensity to receive early invasive management were also the most likely to develop AKI regardless of what strategy they received, suggesting that patient characteristics

(rather than the timing or receipt of invasive procedures) are the most important predictors of AKI.

The diverging risks of AKI and survival associated with early invasive management in our cohort are in keeping with the clinical benefits of angiography and revascularization reported in clinical trials[6;155;156]. Although episodes of AKI have been linked to an increased risk of ESRD[18;20;66], we did not observe a higher risk of ESRD in patients who received early angiography, despite the higher risk of AKI. Radio-contrast associated AKI is usually manifested by a small change in serum creatinine (consistent with the definition of AKI used in our study), rarely leads to acute dialysis (similar to the low risk of AKI requiring dialysis in our study), and is usually reversible[32]. Our findings suggest that such episodes of AKI associated with invasive procedures confer relatively low risks of progression to ESRD, although further studies are needed to determine the risks of progressive kidney disease associated with different forms of AKI.

Our study has several strengths. First, unlike previous observational studies examining the risk of AKI and subsequent clinical outcomes in the setting of PCI, our study included a control group treated with conservative management allowing us to determine the additional risks of events related to management relative to the risks that may occur naturally or due to medical conditions. Second, we used prospectively collected data to minimize misclassification, and adjusted for important prognostic variables including laboratory data to reduce the potential for confounding. Finally, we used a propensity

score matching approach to minimize treatment-by-indication bias in this observational study.

This study has a number of limitations. First, our study was observational in design and thus, unlike a randomized trial, does not prove causal relationships between treatment strategy and outcomes. However, these renal outcomes have not been studied in trials of early invasive versus conservative therapy for ACS, despite multiple observational studies linking AKI to adverse outcomes after coronary procedures. Furthermore, although we used a propensity score analysis to limit the potential for bias, residual confounding due to unmeasured variables may remain. Second, we defined early invasive therapy based on receipt of coronary angiography within 2 days of admission, yet it is possible that some patients for whom an early invasive approach was intended did not receive this strategy for logistical reasons (such as delays in transfer to the hospital with catheterization facilities), or early mortality (died before receiving coronary angiography). However, our results were unchanged in sensitivity analyses which excluded patients who were transferred from another facility or died during the first 2 days of hospitalization, suggesting these limitations were unlikely to have introduced bias.

Third, our study was conducted in a single geographic region in Canada; the availability of cardiac catheterization and rates of revascularization (PCI and CABG) may differ in other settings. Variations in the use of invasive procedures and/or patient populations could alter the relative risk of these outcomes between treatment strategies, although our

results were consistent in several subgroup analyses. Finally, few patients in our study had admission eGFR<30 ml/min/1.73m^2, and a higher risk of AKI could have a larger implication on the risk of acute dialysis and ESRD in this subgroup of patients[10;107;165]. Therefore, further studies are needed to examine renal outcomes, quality of life, and survival with early invasive therapies in these patients.

In conclusion, early invasive management of ACS is associated with a higher risk of AKI than a conservative management approach, but is not associated with higher risks of in-hospital AKI requiring dialysis, or long-term risk of ESRD. Given the improvement in cardiovascular end-points and long-term survival that have been observed with early invasive therapy, these results suggest that invasive therapies should not be postponed or withheld solely because they might increase the risk of AKI.

Table 5.1 - Admission characteristics of patients hospitalized for non-ST elevation acute coronary syndrome participants by treatment approach (Before propensity score matching)

	Before Propensity Score Match			
	Early Invasive (n=4,281)	Conservative (n=6,257)	Std Diff (%)	p value
Demographics				
Age, mean (SD), y	62.5 (12.1)	68.3 (13.6)	-46.2	<0.001
Male sex, %	74.1	70.5	22.5	<0.001
Risk factors				
Diabetes mellitus, %	21.2	26.9	-13.5	<0.001
Hypertension, %	63.0	65.7	-5.7	0.004
Hyperlipidemia, %	75.4	68.8	14.9	<0.001
Cigarette smoker, %	26.0	18.6	17.8	<0.001
Family history CAD, %	41.2	30.4	22.7	<0.001
Comorbidities				
Prior MI, %	21.1	27.4	-14.6	<0.001
Prior PCI, %	21.7	20.7	2.6	0.191
Prior CABG, %	5.8	12.2	-22.6	<0.001
Heart failure, %	3.2	9.9	-27.4	<0.001
Peripheral vascular disease, %	3.2	5.9	-13.3	<0.001
Cerebrovascular disease, %	6.0	8.6	-9.8	<0.001
Charlson comorbidty score, mean (SD)	1.6 (1.8)	2.5 (2.5)	-37.6	<0.001
Admission characteristics				
eGFR, mean (SD), mL/min/1.73m^2	79.5 ()	70.9 ()	36.7	<0.001
Albuminuria, %	19.9	26.3	-15.3	<0.001
Anemia, %	11.2	21.7	-28.5	<0.001
Elevated cardiac enzymes, %	22.8	17.3	13.6	<0.001
Hypotension, %	0.9	1.4	-5.0	0.014
Tachycardia, %	10.4	14.1	-11.3	<0.001
ST deviation, %	6.4	2.4	19.7	<0.001
Hospital characteristics				
Catheterization facility, %	46.6	30.0	35.0	<0.001

Abbreviations: PS = Propensity Score, Angio = Angiography, Med = Medical therapy, Std Diff = Standardized Difference, SD = Standard Deviation, CAD = Coronary Artery Disease, MI = Myocardial Infarction, PCI = Percutaneous Coronary Intervention, CABG = Coronary Artery Bypass Graft, eGFR = estimated Glomerular Filtration Rate.

Std Diff=100 * $(x_{Angio}-x_{Med})/(\sqrt{(s^2_{Angio}+s^2_{Med})/2})$ for continuous variables,
Std Diff=100 * $(p_{Angio}-p_{Med})/(\sqrt{p_{Angio}}\ (1-p_{Angio}+)+p_{Med}\ (1-p_{Med})/2)$ for proportions

Table 5.2 – Predictors of early invasive therapy for patients hospitalized for non-ST elevation acute coronary syndrome participants

	Odds Ratio (95% CI)	p value
Age, (per 10 y)	0.81 (0.78 – 0.85)	<0.001
Male Sex	1.35 (1.22 – 1.48)	<0.001
Diabetes mellitus	1.01 (0.90 – 1.13)	0.849
Hypertension	1.13 (1.03 – 1.24)	0.010
Hyperlipidemia	1.20 (1.09 – 1.33)	<0.001
Cigarette smoker	1.17 (1.05 – 1.30)	0.003
Family history CAD	1.23 (1.13 – 1.35)	<0.001
Prior MI	0.93 (0.82 – 1.05)	0.237
Prior PCI	1.14 (1.01 – 1.28)	0.036
Prior CABG	0.56 (0.47 – 0.66)	<0.001
Heart failure,	0.63 (0.51 – 0.77)	<0.001
Peripheral vascular disease	0.93 (0.74 – 1.16)	0.516
Cerebrovascular disease	1.08 (0.91 – 1.29)	0.353
Charlson comorbidty score		
0/1	Reference	
2/3	0.91 (0.82 – 1.01)	0.086
≥4	0.69 (0.60 – 0.80)	<0.001
Admission eGFR,		
≥60 mL/min/1.73m^2	Reference	
45-59 mL/min/1.73m^2	0.90 (0.79 – 1.01)	0.098
30 – 49 mL/min/1.73m^2	0.63 (0.51 – 0.77)	<0.001
<30 mL/min/1.73m^2	0.19 (0.12 – 0.29)	<0.001
Albuminuria	0.85 (0.76 – 0.94)	0.002
Anemia	0.83 (0.73 – 0.94)	0.004
Elevated cardiac enzymes	1.54 (1.38 – 1.72)	<0.001
Hypotension	0.87 (0.59 – 1.34)	0.565
Tachycardia	0.83 (0.73 – 0.95)	0.007
ST deviation	2.34 (1.88 – 2.93)	<0.001
Catheterization facility	2.12 (1.94 – 2.32)	<0.001

Abbreviations: CAD = Coronary artery disease, MI = myocardial infarction, PCI = Percutaneous coronary intervention, CABG = Coronary artery bypass grafting, eGFR = estimated glomerular filtration rate

Table 5.3 - Admission characteristics of patients hospitalized for non-ST elevation acute coronary syndrome participants by treatment approach (After propensity score matching)

	After Propensity Score Match			
	Early Invasive (n=3,715)	Conservative (n=3,715)	Std Diff (%)	p value
Demographics				
Age, mean (SD), y	63.3 (12.1)	63.5 (13.6)	-1.1	0.633
Male sex, %	71.8	70.5	2.8	0.219
Risk factors				
Diabetes mellitus, %	22.2	22.1	0.3	0.911
Hypertension, %	63.3	62.9	0.8	0.736
Hyperlipidemia, %	74.0	73.3	1.3	0.562
Cigarette smoker, %	24.3	24.0	0.6	0.786
Family history CAD, %	38.7	37.8	2.0	0.403
Comorbidities				
Prior MI, %	21.8	22.6	-2.0	0.372
Prior PCI, %	21.1	21.5	-0.9	0.692
Prior CABG, %	6.5	6.7	-0.8	0.709
Heart failure, %	3.7	3.4	1.1	0.529
Peripheral vascular disease, %	3.3	3.4	-0.6	0.749
Cerebrovascular disease, %	6.1	6.6	-1.9	0.393
Charlson comorbidty score, mean (SD)	1.7 (1.8)	1.8 (2.5)	-1.3	0.544
Admission characteristics				
eGFR, mean (SD), mL/min/1.73m^2	78.2 (22.6)	78.3 (27.4)	-0.4	0.850
Albuminuria, %	20.3	20.7	-0.9	0.687
Anemia, %	12.2	12.3	-0.1	0.972
Elevated cardiac enzymes, %	20.4	18.6	4.4	0.057
Hypotension, %	0.9	0.7	1.5	0.444
Tachycardia, %	11.1	11.7	-1.9	0.402
ST deviation, %	4.5	3.4	5.5	0.012
Hospital characteristics				
Catheterization facility, n (%)	41.4	39.3	4.4	0.065

Abbreviations: PS = Propensity Score, Angio = Angiography, Med = Medical therapy, Std Diff = Standardized Difference, SD = Standard Deviation, CAD = Coronary Artery Disease, MI = Myocardial Infarction, PCI = Percutaneous Coronary Intervention, CABG = Coronary Artery Bypass Graft, eGFR = estimated Glomerular Filtration Rate.

Std Diff=100 * $(x_{Angio}-x_{Med})/(\sqrt{(s^2_{Angio}+s^2_{Med})/2})$ for continuous variables,
Std Diff=100 * $(p_{Angio}-p_{Med})/(\sqrt{p_{Angio}}\ (1-p_{Angio}+)+p_{Med}\ (1-p_{Med})/2)$ for proportions

Propensity score matched using 1-to-1 caliper matching without replacement (caliper with of 0.02 of the log odds of the propensity score)

Table 5.4 – Use of revascularization procedures and outcomes with early invasive versus conservative management among patients hospitalized for non-ST elevation acute coronary syndrome (propensity matched pairs)

	Early Invasive (n=3,715)	Conservative (n=3,715)	Risk Ratio 95% (CI)	p value
Revascularization procedures				
PCI, n (%)	2,045 (55.0)	999 (27.9)	RR 2.05 (1.93 – 2.17)	<0.001
CABG, n (%)	437 (11.8)	160 (4.3)	RR 2.75 (2.31 – 3.28)	<0.001
In-hospital outcomes				
AKI, n (%)	327 (8.8)	215 (5.6)	RR 1.52 (1.29 – 1.80)	<0.001
AKI requiring dialysis, n (%)	12 (0.3)	9 (0.2)	RR 1.33 (0.56 – 3.16)	0.514
Mortality, n (%)	59 (1.6)	65 (1.7)	RR 0.90 (0.64 – 1.29)	0.587
Long-term outcomes				
ESRD, n (%)	26 (0.7)	37 (1.0)	HR 0.71 (0.43 – 1.17)	0.117
Mortality, n (%)	218 (5.9)	271 (7.3)	HR 0.81 (0.68 – 0.96)	0.019

Abbreviations: PCI = Percutaneous coronary intervention, CABG = Coronary artery bypass grafting, AKI = Acute kidney injury, ESRD = End-stage renal disease, RR = Risk ratio, HR = Hazard Ratio

Table 5.5 – Outcomes with invasive (at any time during hospitalization) versus medical management alone among patients hospitalized for non-ST elevation acute coronary syndrome (propensity matched pairs)

	Invasive (n=2,938)	Medical (n=2,938)	Risk Ratio 95% (CI)	p value
In-hospital outcomes				
AKI, n (%)	308 (10.5)	271 (9.2)	RR 1.14 (0.98 – 1.32)	0.098
AKI requiring dialysis, n (%)	15 (0.5)	12 (0.4)	RR 1.25 (0.58 – 2.67)	0.565
Mortality, n (%)	75 (2.5)	129 (4.4)	RR 0.55 (0.39 – 0.77)	0.001
Long-term outcomes				
ESRD, n (%)	40 (1.3)	57 (1.9)	HR 0.67 (045. – 1.01)	0.056
Mortality, n (%)	269 (9.2)	442 (15.1)	HR 0.57 (0.50 – 0.66)	<0.001

Abbreviations: AKI = Acute kidney injury, ESRD = End-stage renal disease, RR = Risk ratio, HR = Hazard Ratio

Figure 5.1 – Distribution of the propensity score for early invasive therapy in patients receiving early invasive versus conservative management in the entire cohort (A), and after propensity score matching (B)

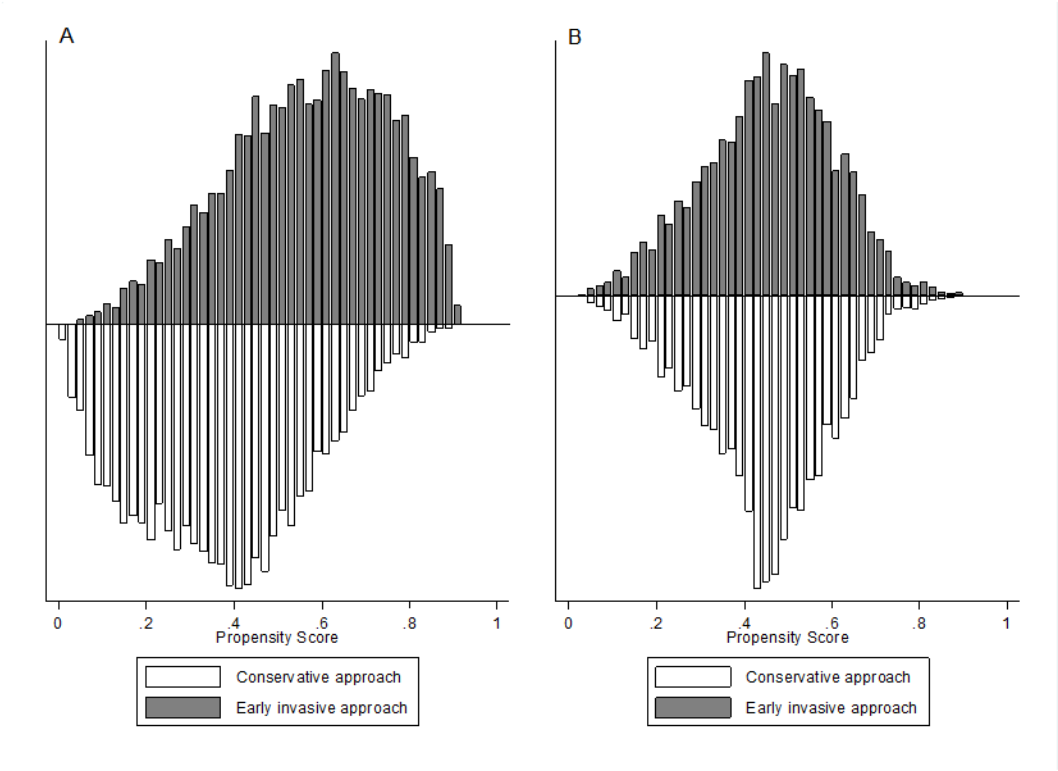


Figure 5.2 – Distribution of the propensity score for invasive management in patients receiving invasive therapy at any time during hospitalization versus medical management in the entire cohort (A), and after propensity score matching (B)

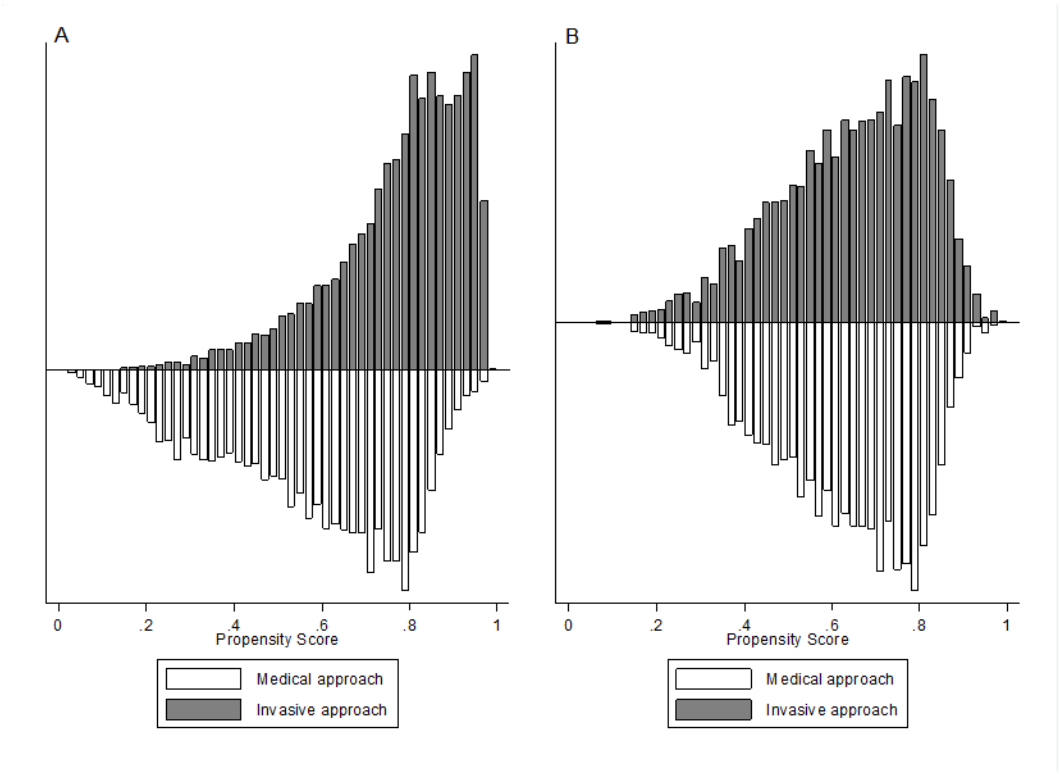


Figure 5.3 – Risks of AKI (A) and death (B) during hospitalization for non-ST elevation acute coronary syndrome by quintile of propensity score and treatment approach (early invasive versus conservative management).

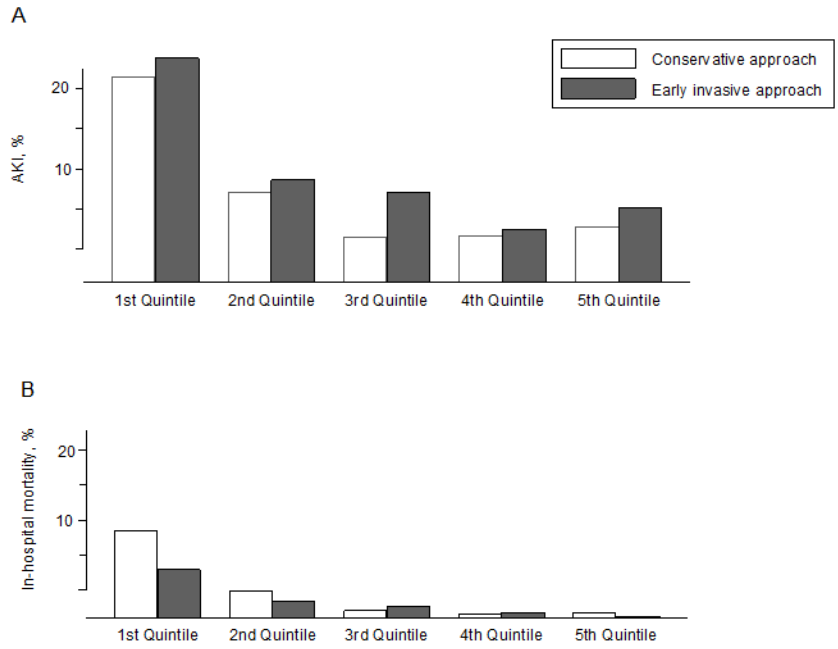
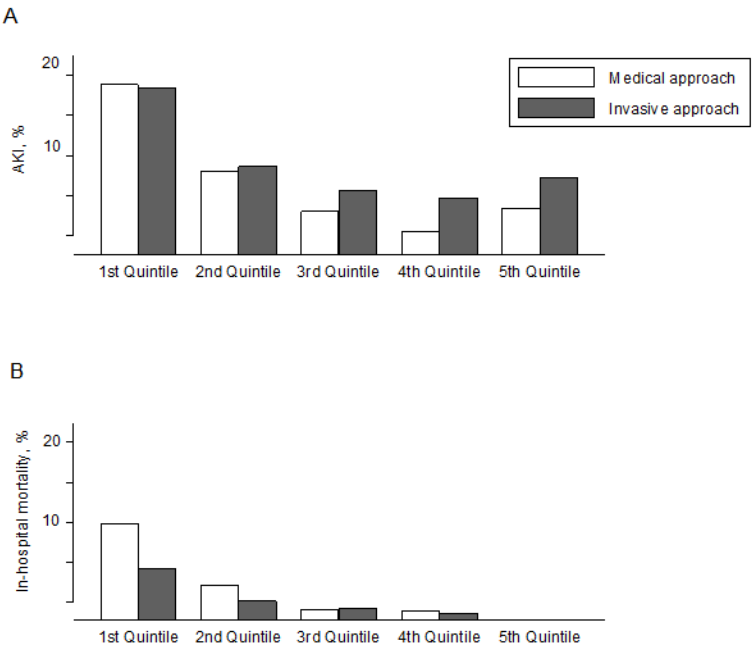


Figure 5.4 – Risks of AKI (A) and death (B) during hospitalization for non-ST elevation acute coronary syndrome by quintile of propensity score and treatment approach (invasive therapy at any time during hospitalization versus medical management alone).



Chapter Six: Summary

6.1 Acute Kidney Injury and Clinical Outcomes after Coronary Angiography

Although AKI following radiocontrast media exposure has traditionally been described as a transient and self-limited condition[32;33], recent studies illustrate associations between AKI and several adverse events after coronary angiography. A systematic review of the literature reveals that many cohort studies have consistently demonstrated longer hospital admissions, higher mortality, and elevated risks of cardiovascular events in those with AKI. By linking a population based registry of patients who received coronary angiography with province-wide laboratory data, we found that patients who developed AKI after coronary angiography were at increased risk of a sustained loss and larger rate of future decline in kidney function. Furthermore, during long-term follow-up, AKI remained associated with death, hospitalization for heart failure, and progression to ESRD. These findings suggest that AKI should not be viewed as a minor complication after angiography and that opportunities may exist to improve outcomes following angiography in patients who develop AKI.

Although we observed several features supportive of a causal relationship between AKI and these clinical outcomes, (including a temporal relationship, dose-response effect, and consistency across studies), these findings should be interpreted with some caution. The true effects of radiocontrast media exposure and AKI in a causal pathway to these outcomes remain unclear[33]. The criteria used to identify the presence and severity of AKI rest upon changes in serum creatinine; however, these do not address the cause of AKI[12;13]. Although AKI after coronary angiography is commonly attributed to the

nephrotoxicity of contrast media, AKI in this setting could result from other processes at play at the time of angiography distinct from radiocontrast media exposure, including patient factors (such as ischemia resulting from low cardiac output[28;33]), or other procedure-related factors (such as atheroembolism as a consequence of vascular catheterization[137]). Accordingly, it is difficult to understand the degree to which death, cardiovascular events and ESRD are attributable to radiocontrast exposure, other procedural aspects of angiography, or patient characteristics. Given this uncertainty it remains controversial whether avoiding radiocontrast agent exposure, preventing AKI, or applying new interventions for AKI could improve these outcomes.

6.2 Renal Outcomes with Early Invasive versus Conservative use of Coronary Angiography

Given that non-procedural and patient-related characteristics are also predictors of AKI after coronary angiography[28;29], and because other mechanisms for AKI (distinct from radiocontrast nephrotoxicity) are plausible, it is unlikely that all episodes of AKI in this setting are attributable to radiocontrast exposure or to coronary angiography itself. This is of clinical relevance because decisions to perform coronary angiography may be influenced by the perceived risks of inducing AKI; despite the fact that non-procedural related factors may be largely influential.

To better understand the effects of coronary angiography upon these risks we compared events in patient groups that differed in their use of coronary angiography during

hospitalization for acute coronary syndrome. We found that patients who received early invasive management experienced a modest increase in risk of AKI during hospitalization compared to those managed conservatively (fewer of whom received coronary angiography). However, early invasive therapy was not associated with an increase in risk of AKI requiring dialysis, ESRD, and, conversely, was associated with better long-term survival. Similar relationships were observed when patients who received coronary angiography were compared with those treated with medical therapy alone. These findings suggest a modest effect for invasive procedures and coronary angiography on the risk of AKI events in this setting, yet no additional effect from these procedures on the risks of dialysis or ESRD. This is in-keeping with the hypothesis that episodes of AKI mediated by other non-procedural causes may be responsible for the adverse outcomes associated with AKI after coronary angiography, although additional studies that differentiate between different forms of AKI are needed to evaluate this hypothesis.

6.3 Implications for Future Research

Regardless of causality, we observed that AKI following coronary angiography does appear to identify a group of patients at higher risk for long-term adverse outcomes including progressive kidney disease, cardiovascular events, ESRD, and death. This suggests that targeting patients who develop AKI for additional management has the potential to improve outcomes. Several therapeutic interventions (eg. anti-platelet agents, beta-blockers, inhibitors of the renin angiotensin system, and statins) have been shown to

be of value in reducing cardiovascular risk, slowing the progression of CKD, and preventing hospital admissions in the general population, as well as in specific populations with coronary artery disease, CKD, and heart failure[37;152;153]. Further research is needed to characterize the comorbidities and features of management of patients who experience AKI in order to identify opportunities where care could be improved. In particular, there is a need to determine whether patients are less likely to receive potentially beneficial interventions such as additional revascularization procedures or medications after an episode of AKI. Furthermore, there is a need to determine whether enhanced clinical follow-up focusing on cardiovascular risk reduction, use of inhibitors of the renin-angiotensin system, or management of kidney disease related complications has the potential to improve outcomes following an episode of AKI.

Given the benefits seen with coronary angiography in unstable coronary disease, and the observation that the most clinically important renal outcomes of dialysis and ESRD were similar regardless of timing or use of coronary angiography in this setting, it is unlikely that practices of delaying or restricting the use of invasive coronary procedures in patients at risk of AKI will improve clinical outcomes. Accordingly, there is a need for randomized clinical trials that evaluate the effects of additional preventive therapies in the setting of coronary angiography, as well as other high risk groups of hospitalized patients with acute coronary syndromes. To date, the outcomes of prevention trials in the setting of coronary angiography have relied on surrogate outcomes in the form of small

changes in serum creatinine concentration between 2 to 5 days after angiography. Whether the prevention of these small changes in kidney function modifies the risks of important clinical outcomes remains uncertain. Large clinical trials of prophylactic interventions, powered to detect differences in risk of death, cardiovascular events, dialysis and ESRD should be the focus of such future studies.

6.4 Conclusion

In conclusion, AKI after invasive coronary angiography is associated with increased risks of long-term loss of kidney function, further hospital admissions for cardiovascular and renal events, progression to ESRD, and mortality. Episodes of AKI could be used to identify high risk patients, prompt additional follow-up, and guide further management. Further research is needed to identify interventions that, either by preventing AKI or enhancing post-AKI management, lead to improved long-term outcomes. Although invasive management approaches for acute coronary syndromes are associated with a modest increase in risk of AKI, they do not appear to increase the risks of in-hospital AKI requiring dialysis, or long-term risk of ESRD. Given the improvement in cardiovascular outcomes and long-term survival that have been observed with early invasive therapy, these results suggest that postponing or withholding invasive therapies simply to reduce the risk of AKI is unlikely to improve clinical outcomes.

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