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Secular Trends in Cardiovascular Disease in Kidney Transplant Recipients: 1994 to 2009

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

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(Thesis format: Monograph)

by

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Abstract

Cardiovascular events are a major cause of morbidity and mortality in kidney transplant recipients. We conducted a retrospective study using healthcare databases in Ontario, Canada to determine whether the incidence of cardiovascular events has changed from 1994 to 2009 in 4954 kidney transplant recipients. Our primary endpoint was a 3-year composite outcome of post-transplant death or cardiovascular event (myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft, or stroke). Recipients were older and had more baseline co-morbidity in recent eras (1994-1997 vs. 2006-2009: median age 45 vs. 53 years; coronary artery disease 22% vs. 37%). A total of 445 recipients (9.0%) died or experienced a cardiovascular event within 3 years. There was no significant change in the composite outcome or death-censored cardiovascular events (p=0.41 and 0.92, respectively) over time. Despite transplant centers accepting recipients who are older with more co-morbidities, the incidence of death or cardiovascular event has remained stable.

Keywords

administrative data, cardiovascular disease, coronary artery bypass graft, health outcomes, kidney transplant recipients, myocardial infarction, percutaneous coronary intervention, retrospective cohort study, stroke, trends.

Co-Authorship Statement

The study presented here was designed and executed by Ngan N. Lam. This includes, but is not limited to, study conception, data creation plan (DCP) production (**Appendix 1**), data analysis, and manuscript production and editing. The supervisory committee as well as each of the co-authors provided regular feedback.

Dr. Amit Garg was the primary supervisor and was involved in all aspects of the work. I would like to acknowledge the other co-authors and reviewers who helped edit the final manuscript.

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List of Abbreviations

aHR	Adjusted Hazard Ratio
ANZDATA	Australia and New Zealand Dialysis and Transplant
CABG	Coronary Artery Bypass Graft
CI	Confidence Interval
CIHI-DAD	Canadian Institute for Health Information Discharge Abstract Database
CKD	Chronic Kidney Disease
CORR	Canadian Organ Replacement Register
ESRD	End-Stage Renal Disease
GFR	Glomerular Filtration Rate
ICD-9 CM	International Classification of Disease Canadian Modified system
ICD-10 CA	International Classification of Disease 10th version, Canada
ICES	Institute for Clinical Evaluative Sciences
IQR	Interquartile Range
KDIGO	Kidney Disease: Improving Global Outcomes
NKF-KDOQI	National Kidney Foundation-Kidney Disease Outcomes Quality Initiative
OHIP	Ontario Health Insurance Plan
OR	Odds Ratio
PCI	Percutaneous Coronary Intervention
PMP	Per Million Population

RPDB	Registered Persons Database
RRT	Renal Replacement Therapy
SAS	Statistical Analysis Software
TIA	Transient Ischemic Attack
U.S.	United States
USRDS	United States Renal Data System

Chapter 1 : Introduction

1.1 Background

Compared to dialysis, kidney transplantation improves survival.(1–3) Cardiovascular disease accounts for 30% of deaths with a functioning graft and remains the primary cause of death in kidney transplant recipients.(4) As described in recent clinical practice guidelines, kidney transplant recipients are a high-risk group for cardiovascular disease.(5,6) For example, in a retrospective study of 36,000 kidney transplant recipients between 1995 and 2000 identified in the United States Renal Data System (USRDS) database, 1 in 10 first-time kidney transplant recipients (11%) had a myocardial infarction in the subsequent 3 years.(7) In recent years, a greater proportion of individuals receiving kidney transplants are older and have more co-morbidities, including pre-transplant cardiovascular disease and diabetes mellitus.(8) We conducted this study to assess whether these secular changes have resulted in an increased risk of cardiovascular events after kidney transplantation over time.

1.2 Objectives

The specific aims of this research project were as follows:

1) To describe the secular trends in the 3-year cumulative incidence of death or first major cardiovascular event after receiving a kidney transplant for recipients from 1994 to 2009.
2) To describe the secular trends in the individual components of the above composite outcome, specifically, the 3-year cumulative incidence of a) death and b) death-censored major cardiovascular event in kidney transplant recipients.
3) To compare the above trends in the kidney transplant recipient population to that in the general population over the same time period.

Chapter 2 : Literature Review

2.1 Chronic Kidney Disease (CKD)

In 2002, the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) developed a definition and classification system for chronic kidney disease (CKD).(9) In these guidelines, CKD was defined based on the presence of kidney damage due to structural or functional abnormalities and/or kidney dysfunction as measured by a glomerular filtration rate (GFR) of <60 mL/min/1.73 m^2 for at least 3 months (**Table 1**).

Table 1: Stages of chronic kidney disease.[a]

Stage	Description	GFR (mL/min/1.73 m^2)
1	Kidney damage with normal or high GFR	≥90
2	Kidney damage with mild decrease in GFR	60-89
3	Moderate decrease in GFR	30-59
4	Severe decrease in GFR	15-29
5	Kidney failure	<15 (or RRT)

[a] Adapted from the NKF-KDOQI guidelines.(9)
Abbreviations: GFR, glomerular filtration rate; NKF-KDOQI, National Kidney Foundation-Kidney Disease Outcomes Quality Initiative; RRT, renal replacement therapy.

2.2 End-Stage Renal Disease (ESRD)

Definition of ESRD

End-stage renal disease (ESRD) (CKD Stage 5) is defined as either a GFR of <15 mL/min/1.73 m^2 or the need for renal replacement therapy (RRT; see Section 2.3) for symptoms or complications of kidney failure (**Table 1**).(9) The Canadian Organ Replacement Register (CORR) collects information on patients with kidney failure and their subsequent treatments.(10) CORR defines ESRD as patients who receive treatment for their kidney failure with either ongoing dialysis or a kidney transplant.

Epidemiology of ESRD

Prevalence is defined as the number of total cases at a point in time divided by the size of the overall population. Incidence is defined as the number of new cases during a given period divided by the size of the at-risk population. The rate per million population (PMP) per year is calculated as (number of cases / population) x 1,000,000.

According to CORR, in 2012, there were 41,252 prevalent cases of ESRD in Canada and this number has increased by 40% from 29,540 in 2003.(10) Older patients (≥65 years old) represent approximately 40% of prevalent cases of ESRD and the proportion of males is 60%. Diabetes mellitus remains the primary cause of ESRD (27%) followed by glomerulonephritis (i.e. inflammation of the kidneys usually due to an immunological disease; 22%).

In 2012, there were 5431 incident cases of ESRD for an incidence rate of 156 PMP.(10) Although the incidence rate is higher than it was in 1993 (incidence rate of 101 PMP), it has remained stable over the last decade (in 2003, incidence rate was 162 PMP). Older patients (≥65 years old) represent more than half of new cases each year. The primary cause of ESRD is diabetes mellitus accounting for approximately 38% of new cases, followed by renal vascular diseases (15%) such as hypertension.

2.3 Renal Replacement Therapy (RRT)

Definition of RRT

The treatment for patients with kidney failure is commonly referred to as renal replacement therapy (RRT). The most common form of RRT is dialysis, which consists of either hemodialysis or peritoneal dialysis. Dialysis acts as an artificial kidney, removing waste products and excess water from the body. The second form of RRT is kidney transplantation for which the organ can be from either a living donor or a deceased donor.

Epidemiology of RRT

Overall, in 2012, the proportion of patients with ESRD on dialysis was 58% (n=23,814) of which approximately 50% were on hemodialysis and 10% were on peritoneal dialysis.(10) The remaining 42% (n=17,438) of patients with ESRD had a functioning kidney transplant and this rate has increased from 222 PMP in 1993 to 500 PMP in 2012. The proportions of patients on dialysis (approximately 60%) or with a functioning kidney transplant (approximately 40%) have not changed dramatically in the last decade. The highest number of kidney transplant surgeries in Canada is performed in Ontario.

The majority of patients who start treatment for their ESRD are initiated on hemodialysis (79%), followed by peritoneal dialysis (18%), then pre-emptive kidney transplantation (i.e. receipt of a kidney transplant without receiving dialysis first; 3%).(10) In Canada, these proportions have remained fairly stable over time from 2003 to 2012.

2.4 Outcomes in Dialysis Versus Kidney Transplantation

There have been many studies comparing the different types of RRT and survival for patients with ESRD.(1–3,11) In a longitudinal study by Wolfe *et al*., kidney transplant recipients in the United States (U.S.) had a 2.8-fold higher relative risk of death in the first 2 weeks of their surgery compared to patients who remained on the waiting list for a transplant.(1) This was likely due to peri-operative surgical risks as well as risks associated with initial high-dose immunosuppression used for induction and maintenance therapy. At 18 months, the relative risk of death in kidney transplant recipients compared to patients on the waiting list was significantly lower (relative risk 0.32; 95% confidence interval [CI] 0.30 to 0.35; $p<0.001$). The survival benefit was observed across all ages (including older recipients), both sexes, all races, and for all causes of ESRD but was greatest amongst recipients who were younger, Caucasian, or had diabetes mellitus as the cause of their ESRD. Similar results were observed in a cohort of patients with ESRD from Ontario, Canada.(3) The 5-year patient survival is higher with a kidney from a living donor (94%) than with a kidney from a deceased donor (76%) and both are higher than remaining on chronic dialysis (60%). In addition to greater long-term survival, kidney transplantation is also associated with improved quality of life and lower healthcare costs compared to remaining on dialysis.(12–16) For all these reasons, in eligible patients with ESRD, kidney transplantation is the preferred treatment modality.

2.5 Cardiovascular Disease in Kidney Transplant Recipients

While the risk of cardiovascular death is significantly lower with kidney transplantation compared to dialysis, the risk remains higher than the general population even after stratifying by age, sex, and race.(17,18) According to the 2014 United States Renal Data System (USRDS) Annual Report, cardiovascular disease remains the primary identified

cause of death in kidney transplant recipients.(4) It accounts for almost 30% of deaths with a functioning graft.

Unfortunately, there is limited information regarding the incidence of non-fatal cardiovascular events post-transplantation. One study using the USRDS followed almost 36,000 kidney transplant recipients between 1995 to 2000 and found that the 3-year cumulative incidence of post-transplant myocardial infarction was 11%.(7) The occurrence of a myocardial infarction predicted graft failure (hazard ratio 1.9; 95% CI 1.6 to 2.2) and death.

Another study using the USRDS compared female kidney transplant recipients between 1987 to 1994 whose ESRD was due to lupus nephritis (n=946), diabetes mellitus (n=5173), or other causes (n=12,733).(19) After a median follow-up of 2.5 years, and after adjusting for age and race, the incidence rate of post-transplant myocardial infarction was similar in women with lupus nephritis as their cause of ESRD compared to women with other causes for ESRD (5.7 per 1000 patient-years for women with lupus nephritis vs. 3.1 per 1000 patients years for women with other causes; adjusted hazard ratio [aHR] 1.67; 95% CI 0.86 to 3.23; p=0.13). The adjusted incidence rate was highest in women with diabetes mellitus as their cause of ESRD compared to women with other causes for ESRD (10.0 per 1000 patient-years; aHR 3.31; 95% CI 2.59 to 4.22; $p<0.0001$). These incidence rates in kidney transplant recipients were lower than in the women who remained on dialysis.

Another retrospective cohort study using the Netherlands Organ Transplantation Registration database followed 2187 kidney transplant recipients between 1984 to 1997 and reported that the cumulative incidence of post-transplant cardiovascular events (myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, cerebrovascular accident, and cardiovascular death) was 40%.(20) The incidence of cardiovascular events was highest in the first 3 months after transplantation (4%). Although the median follow-up was 8 years (interquartile range 4.5 to 11.4), this study only included recipients transplanted before 1997 and may not reflect current patient characteristics or clinical practice patterns.

Similarly, a smaller study from Germany compared 46 patients with type I diabetes mellitus who received a kidney transplant between 1978 to 1997 to 46 patients with type I diabetes mellitus who were on the waiting list for a transplant but remained on hemodialysis.(11) Recipients and dialysis patients were matched 1:1 on age, sex, duration of diabetes mellitus, dialysis vintage (duration on dialysis), and waitlist duration. After a mean follow-up time of 6 years, kidney transplant recipients had a significantly lower risk of myocardial infarction (9% vs. 28%; odds ratio [OR] 0.24; 95% CI 0.07 to 0.81; p=0.03) and coronary angioplasty (9% vs. 33%; OR 0.20; 95% CI 0.06 to 0.65; p=0.008) compared to hemodialysis patients.

2.6 Cardiac Risk Factors in Kidney Transplant Recipients

Kidney transplant recipients have a unique combination of traditional cardiovascular risk factors and renal-specific cardiovascular risk factors.(21) Traditional cardiovascular risk factors include hypertension, diabetes mellitus, hyperlipidemia, smoking, older age, obesity, and physical inactivity.(22) Renal-specific associative factors include decreased renal function (compared to the general population), immunosuppressive medications, episodes of rejection and graft loss, and donor type (living versus deceased donors).(20,23,24) These factors are often interrelated and thus, it can be difficult to isolate the effects of a single risk factor on cardiovascular outcomes. For example, although a kidney transplant improves the recipient's renal function, there is often residual renal impairment that can cause or exacerbate other cardiovascular risk factors such as hypertension.(21) In some studies, decreased renal function has been shown to be an independent risk factor for cardiovascular disease.(25–28) Similarly, long-term immunosuppressive medications, such as steroids and calcineurin-inhibitors, used to prevent and treat rejection may cause or worsen hypertension, diabetes mellitus, and renal impairment.(23) For these reasons, the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines suggest that kidney transplant recipients be considered to be at the highest risk for cardiovascular disease.(5)

2.7 Secular Trends in Cardiovascular Disease

There have been several advances in the screening and management of cardiovascular disease in the CKD population.(29) In addition to this, the baseline characteristics of accepted recipients has changed over time.(8,30) Unfortunately, there is a lack of literature regarding how these secular changes have affected cardiovascular outcomes after kidney transplantation. One study from 2001 used the USRDS to follow a cohort of 104,000 patients on the kidney transplant waiting list between 1988 to 1996, of which 73,707 patients subsequently received a transplant.(31) For transplanted patients, the 5-year annual adjusted cardiovascular death rate per 1000 patients decreased linearly from 19.2 in 1989 to 9.1 in 1996. A similar trend for cardiovascular death was seen in waitlisted patients (65 in 1989 to 46 in 1996) and in the general population (1.6 in 1989 to 1.3 in 1996). Thus, cardiovascular death in kidney transplant recipients improved over the study period and was lower than those on the waitlist, although it still remained higher than the general population.

In 2007, another study using the Australia and New Zealand Dialysis and Transplant (ANZDATA) registry reported trends over time in 6764 kidney transplant recipients.(8) From 1993 to 2004, there was a trend towards older recipients, higher recipient body mass index, and longer waiting time in recent cohorts. There was also a significant increase in baseline recipient co-morbidities including cardiovascular disease and diabetes mellitus (assessed at the start of renal replacement therapy). As in the previous study, cardiovascular death decreased over time, despite the increase in recipient cardiovascular co-morbidities, likely due to improved management over time of cardiovascular risk factors and outcomes. In both studies, the outcome of non-fatal cardiovascular events was not reported.

2.8 Limitations of the Current Literature

Given the significance of cardiovascular disease in the kidney transplant population, information regarding secular trends in cardiovascular outcomes and clinical practices would better inform transplant centers and patients. Unfortunately, there are major knowledge gaps in the literature and prior studies have significant limitations:

1) Much of the literature on cardiovascular outcomes using transplant registries focuses on cardiovascular mortality rather than non-fatal cardiovascular events. We know little about the secular trends in non-fatal cardiovascular events in the kidney transplant population despite the increase in recipient cardiovascular co-morbidities over time.(31)

2) Pre-transplant baseline co-morbidities are often inadequately captured.(8)

3) Previous studies prior to 2000 have a cohort of recipients that may not be representative of the current kidney transplant population.(30)

4) The largest studies assessing cardiovascular outcomes have used the USRDS (U.S. data) and there is a need to understand the trends in a Canadian kidney transplant population.(7,31)

Ontario residents receive universal access to hospital and physician services and coverage for medical services are from a single provincial payer system. The unique linked healthcare administrative databases at the Institute for Clinical Evaluative Sciences (ICES) can be used to generate new information that addresses the limitations of previous studies described above. This comprehensive administrative database has been used in previous studies to assess trends in renal and cardiovascular outcomes and its strengths are internationally recognized.(32,33)

Chapter 3 : Methodology

3.1 Design and Setting

We conducted a population-based retrospective cohort study using linked healthcare databases via unique, encoded identifiers held at the Institute for Clinical Evaluative Sciences (ICES) in Ontario, Canada. Ontario is the most populous Canadian province with approximately 13 million residents who all have universal access to hospital care and physician services. The reporting of this study follows guidelines set out for observational studies (**Appendix 2**)(34), and was conducted according to an established protocol approved by the research ethics board at Sunnybrook Health Sciences Centre (Toronto, Canada).

3.2 Data Sources

We ascertained baseline characteristics, covariate information, and outcome data from records in 4 databases.

Canadian Organ Replacement Register (CORR) Database

Kidney transplant recipients were identified from the CORR database that captures all dialysis and kidney transplant activity in Canada. Compared to information collected at the transplant centers, CORR accurately identified kidney transplant recipients with a sensitivity of 96% (95% confidence interval [CI] 94% to 97%) and a positive predictive value of 98% (95% CI 98% to 99%).(35)

Registered Persons Database (RPDB)

The RPDB captured demographic information such as date of birth, sex, postal code, and vital status (such as death).

Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD)

Diagnostic and procedural information during hospital admissions was gathered from the CIHI-DAD. Coding of primary and secondary diagnoses and inpatient procedures used the 9th version of the International Classification of Disease Canadian Modified system (ICD-9 CM) prior to 2002 and the 10th version, Canada (ICD-10 CA) for all diagnoses after 2002. We used this database to determine co-morbid conditions prior to transplantation, assess cardiovascular outcomes, and identify potential confounders.

Ontario Health Insurance Plan (OHIP) Database

Physicians in Ontario may submit billing claims for reimbursement to the OHIP using diagnostic and fee codes for every inpatient, outpatient, and laboratory service rendered to a patient. We used this database to ascertain our primary outcome of cardiovascular events.

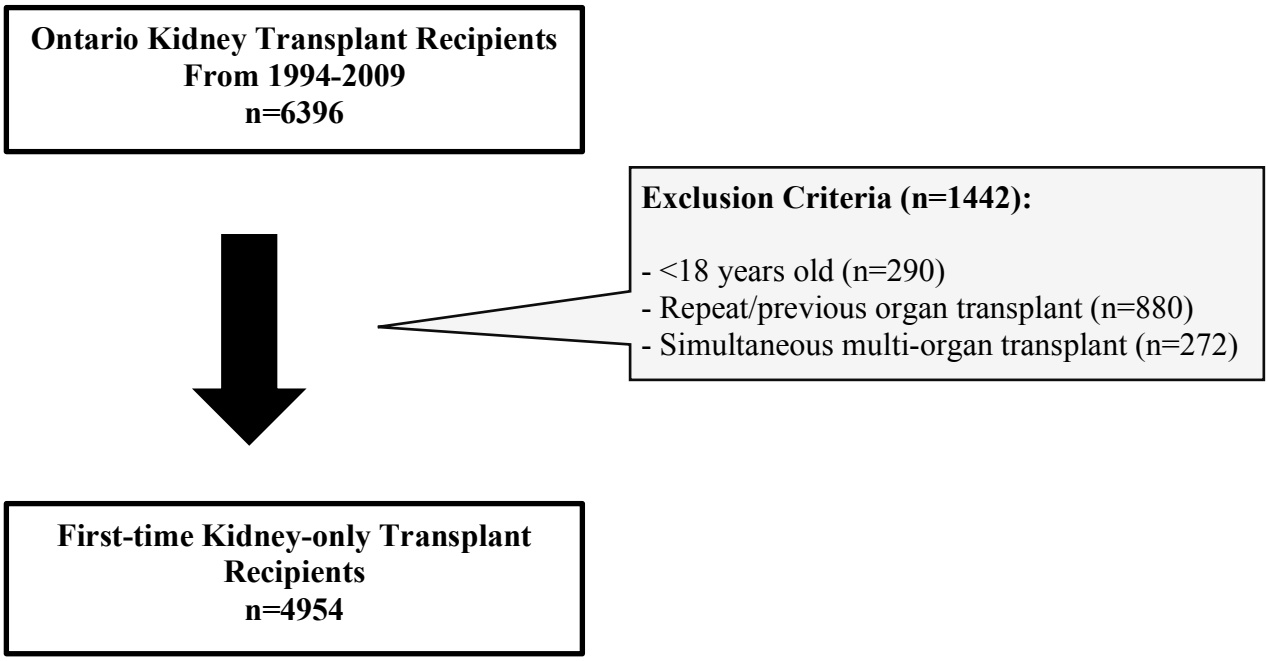
These databases have been used extensively for research on health outcomes and services including studies on cardiovascular disease.(32,36–43) The majority of the data were complete with the exception of income (0.3% missing), donor status (1% missing), primary cause of end-stage renal disease (ESRD, 8% missing), and race (10% missing).

3.3 Population: Kidney Transplant Recipients

We included all adult recipients who were permanent residents of Ontario and received their first kidney-only transplant between January 1, 1994 and December 31, 2009 from 1 of the 6 major transplant centers in Ontario. The 6 major transplant centers included London Health Sciences Centre, St. Joseph's Healthcare System (Hamilton), University Health Network (Toronto), St. Michael's Hospital (Toronto), Kingston General Hospital, and Ottawa General Hospital. Only those kidney transplants performed at The Hospital for Sick Children (Toronto) were excluded from the study since our study population only consisted of adult kidney transplant recipients. The date of their transplant served as the start date for follow-up and was designated the 'index date'. The year of kidney transplantation represented the primary exposure of interest.

We excluded pediatric recipients (<18 years old) at the time of transplant and those who had received a previous organ transplant or a simultaneous multi-organ transplant, including kidney-pancreas. Multi-organ transplants are uncommon compared to single-organ transplants, with simultaneous kidney-pancreas transplantation comprising only 4% of all kidney transplantations done in Ontario in the last 10 years,(10); cardiovascular outcomes also differ in this population compared to kidney-only transplantation.(44) A diagram of the kidney transplant recipient cohort selection is presented in **Figure 1**.

Figure 1: Cohort selection.



3.4 Population: General Population

We randomly assigned an index date to the entire adult general population in Ontario, Canada according to the distribution of index dates in recipients. As in the recipients, we excluded residents who were <18 years old on their assigned index date and looked back to the beginning of the databases (January 1981 for CORR) to exclude individuals with chronic kidney disease (CKD; including those who previously received dialysis or a kidney transplant). Kidney transplant recipients were then matched to the general population based on age (±1 year), sex, and index date (±6 months) using a 1:4 ratio. No recipients were lost in the matching process.

3.5 Primary Outcome

The primary outcome was a composite of death or first major cardiovascular event within 3 years of the index date. A major cardiovascular event was defined as a hospitalization where the primary diagnosis was myocardial infarction or ischemic stroke, or evidence of a procedural code for percutaneous coronary intervention or coronary artery bypass graft surgery. Previous studies in the non-transplant and transplant population have used similar cardiovascular outcomes.(20,28,38,45) These diagnostic and procedural codes have also been shown to have good validity when compared with chart review (**Appendix 3**). A 3-year follow-up period was chosen in order to compare results to the U.S. population where Medicare coverage lasts for only 3 years following transplantation. In addition to this, our estimates of cardiovascular incidence could be used to inform sample size calculations for future clinical trials.

3.6 Additional Outcomes

Additional outcomes include the components of the primary outcome analyzed separately [i) death and ii) death-censored major cardiovascular event]. We also examined the proportion of recipients who received cardiac investigations in the 3 years following transplantation. To better inform peri-operative outcomes, we assessed the 30-day cumulative incidence of myocardial infarction and ischemic stroke (where hospital diagnostic codes were not limited to the primary diagnosis).

3.7 Statistical Analysis

We conducted all analyses with SAS (Statistical Analysis Software) version 9.3 (SAS Institute Inc., Cary, NC). All patients were followed until the outcome of interest or the end of the study period (December 31, 2012). We continued to follow all kidney transplant recipients even if they experienced graft failure (i.e. recipients were followed

for the outcome of interest even if they returned to chronic dialysis or received a re-transplant during the 3-year follow-up period).

Baseline Characteristics

Starting the cohort in 1994 allowed for a minimum of 3 years in the look-back window to assess for baseline co-morbidities since the CIHI-DAD and OHIP databases were only available from 1991 onwards. We categorized the study period into 4-year eras and grouped recipients based on their index dates: 1994-1997, 1998-2001, 2002-2005, and 2006-2009. We reported continuous baseline characteristics as means with standard distributions for data that was normally distributed or as medians with interquartile range for data that was skewed. Categorical variables were reported as proportions. Distributions of baseline characteristics among patients within each era were compared using the Chi-square test for categorical variables and ANOVA for continuous variables.

Primary Analyses

Having the accrual period end in 2009 allowed for a minimum of 3 years of follow-up to assess for outcomes since, at the time of analysis, the CIHI-DAD and OHIP databases were updated until 2012. We assessed changes in the 3-year cumulative incidence of cardiovascular events over time using the Cochran-Armitage test for trend. We reported the 95% confidence intervals for the cumulative incidences using the Wilson score method. We used Cox proportional hazard analyses to examine the association between transplant era and outcome, adjusting for age, sex, and a history of coronary artery disease, myocardial infarction, hypertension, and diabetes mellitus at the time of transplant (referent era was 1994-1997).

Subgroup Analyses

We repeated the primary analysis in 3 pre-specified subgroups: age at transplantation (<65 vs. ≥65 years), sex (males vs. females), and donor type (living vs. deceased; the 1% with missing values were not included in the analysis).

Additional Analyses

We also calculated the incidence rate defined as the rate per 100 person-years of follow-up. We hypothesized that the incidence rate for the primary outcome would be highest in the early peri-operative period. To test this hypothesis, for each era, we performed unadjusted serial Poisson models for the following time periods after transplantation: 0-3 months, 4-12 months, and 13-36 months. Among recipients who experienced an event within the first 3 years of transplantation, we also assessed the time to the first qualifying event after transplantation. Given the small number of anticipated events for the 30-day outcomes of myocardial infarction and ischemic stroke, we reported only the cumulative incidence for the entire cohort.

Chapter 4 : Results

4.1 Baseline Characteristics: Kidney Transplant Recipients

Baseline characteristics for 4954 kidney transplant recipients are presented in **Table 2**. When recipients were followed for a maximum of 3 years, the total follow-up was 14,096 person-years. Overall, 63% of recipients were males and glomerulonephritis was the main cause of end-stage renal disease (ESRD) throughout the study period (35% for the entire cohort). The median time on dialysis prior to transplantation was 2 years (interquartile range [IQR] 1 to 4) and 41% of recipients received a kidney from a living donor.

The age and co-morbidity of kidney transplant recipients increased during the study period. The median age at transplantation increased from 45 years (IQR 35 to 55) in 1994-1997 to 53 (IQR 42 to 62) in 2006-2009 ($p<0.001$). Comparing the era 1994-1997 to 2006-2009, the proportion of recipients aged 65 years and older increased (from 5.7% to 17%; $p<0.001$), as did the proportion of recipients with pre-transplant coronary artery disease (from 22% to 37%; $p<0.001$) and diabetes mellitus (from 21% to 29%; $p<0.001$). The proportion of recipients undergoing cardiovascular investigations in the 3 years prior to transplantation increased dramatically across the eras. For example, the proportion of recipients receiving an echocardiogram increased from 76% in 1994-1997 to 96% in 2006-2009 ($p<0.001$). Similarly, the proportion of recipients receiving a pre-transplant coronary angiogram more than doubled from 9.5% in 1994-1997 to 21% in 2006-2009 ($p<0.001$).

Table 2: Baseline characteristics of kidney transplant recipients in Ontario by era.

Characteristic	Total n=4954	1994-1997 n=1048	1998-2001 n=1110	2002-2005 n=1182	2006-2009 n=1614	p value[a]
Age (years)	49 [38-59]	45 [35-55]	47 [36-57]	51 [41-60]	53 [42-62]	
<65	4345 (88)	988 (94)	1004 (90)	1016 (86)	1337 (83)	<0.001
≥65	609 (12)	60 (5.7)	106 (9.5)	166 (14)	277 (17)	
Male	3120 (63)	664 (63)	681 (61)	759 (64)	1016 (63)	0.55
Race						
Caucasian	3385 (68)	800 (76)	784 (71)	796 (67)	1005 (62)	
Asian	321 (6.5)	66 (6.3)	67 (6.0)	66 (5.6)	122 (7.6)	
African-American	276 (5.6)	42 (4.0)	54 (4.9)	69 (5.8)	111 (6.9)	<0.001
Indian	268 (5.4)	52 (5.0)	54 (4.9)	65 (5.5)	97 (6.0)	
Other	222 (4.5)	22 (2.1)	32 (2.9)	51 (4.3)	117 (7.2)	
Unknown	482 (9.7)	66 (6.3)	119 (11)	135 (11)	162 (10)	
Income quintile[b]						
Lowest	1088 (22)	235 (22)	219 (20)	264 (22)	370 (23)	
Middle	990 (20)	207 (20)	219 (20)	240 (20)	324 (20)	0.80
Highest	933 (19)	190 (18)	231 (21)	230 (20)	282 (17)	
Urban residence[c]	4367 (88)	920 (88)	968 (87)	1051 (89)	1428 (88)	0.15
Cause of ESRD						
Glomerulonephritis	1733 (35)	416 (40)	418 (38)	391 (33)	508 (31)	
Diabetes mellitus	900 (18)	153 (15)	196 (18)	220 (19)	331 (21)	
Cystic	656 (13)	120 (11)	148 (13)	170 (14)	218 (14)	<0.001
Vascular	518 (10)	92 (8.8)	97 (8.7)	141 (12)	188 (12)	
Other	759 (15)	158 (15)	167 (15)	201 (17)	233 (14)	
Unknown	388 (7.8)	109 (10)	84 (7.6)	59 (5.0)	136 (8.4)	
Donor type						
Deceased	2839 (57)	667 (64)	605 (55)	643 (54)	924 (57)	
Living	2048 (41)	348 (33)	492 (44)	531 (45)	677 (42)	<0.001
Unknown	67 (1.4)	33 (3.1)	13 (1.2)	8 (0.7)	13 (0.8)	
Pre-transplant dialysis modality						
Pre-emptive[d]	446 (9.0)	66 (6.3)	107 (9.6)	101 (8.5)	172 (11)	
Hemodialysis	2978 (60)	544 (52)	673 (61)	764 (65)	997 (62)	<0.001
Peritoneal	1530 (31)	438 (42)	330 (30)	317 (27)	445 (28)	
Dialysis vintage (years)	2 [1-4]	2 [1-4]	2 [1-4]	3 [1-5]	3 [1-6]	<0.001

Delayed graft function[e]	1331 (27)	283 (27)	292 (26)	296 (25)	460 (29)	0.22
Primary non-function[f]	389 (7.9)	88 (8.4)	71 (6.4)	90 (7.6)	140 (8.7)	0.15
Co-morbidities[g]						
Coronary artery disease	1527 (31)	235 (22)	312 (28)	410 (35)	597 (37)	<0.001
Hypertension	3670 (74)	820 (78)	859 (77)	871 (74)	1120 (69)	<0.001
Diabetes mellitus	1275 (26)	224 (21)	267 (24)	323 (27)	461 (29)	<0.001
Myocardial infarction	99 (2.0)	13 (1.2)	17 (1.5)	32 (2.7)	37 (2.3)	0.045
PCI	115 (2.3)	9 (0.9)	15 (1.4)	30 (2.5)	61 (3.8)	<0.001
CABG surgery	119 (2.4)	11 (1.0)	21 (1.9)	38 (3.2)	49 (3.0)	0.001
Heart failure	692 (14)	171 (16)	160 (14)	167 (14)	194 (12)	<0.001
Stroke/TIA	67 (1.4)	13 (1.2)	21 (1.9)	14 (1.2)	19 (1.2)	0.37
Cardiovascular investigations[g]						
Holter monitor	483 (9.7)	83 (7.9)	103 (9.3)	117 (9.9)	180 (11)	0.048
Echocardiography	4388 (89)	801 (76)	956 (86)	1081 (91)	1550 (96)	<0.001
Stress test	3567 (72)	518 (49)	718 (65)	947 (80)	1384 (86)	<0.001
Coronary angiogram	831 (17)	100 (9.5)	164 (15)	235 (20)	332 (21)	<0.001
Carotid ultrasound	885 (18)	146 (14)	180 (16)	256 (22)	303 (19)	<0.001

Data presented as number (percentage) or median [interquartile range].

[a] Chi-square test for categorical variables and ANOVA for continuous variables (e.g. age, dialysis vintage).

[b] Income was categorized according to fifths of average neighborhood income, with the first quintile calculated as the lowest income and the fifth quintile as the highest income. Missing values (0.3%) were categorized into the middle quintile.

[c] Urban location indicates a population >10,000.

[d] Recipients identified as pre-emptive in the Canadian Organ Replacement Register were assessed for the presence of dialysis codes and re-classified as hemodialysis (n=26) or peritoneal dialysis (n=35).

[e] Delayed graft function was defined as a dialysis code within the first 7 days of transplantation.

[f] Primary non-function was defined as 3 dialysis codes on 3 separate days with at least 1 dialysis code appearing in the first 7 days of transplantation, between day 8 and 30 of transplantation, and between day 31 and 60 of transplantation.

[g] Assessed by the presence of a diagnostic or procedural code in the 3 years prior to the transplant except for hypertension and diabetes mellitus which are defined as the presence of either 2 OHIP codes or 1 hospitalization with a diagnosis of hypertension or diabetes mellitus, respectively, in the 3 years prior to the transplant (an algorithm previously validated for hypertension and diabetes mellitus).(46,47)

Abbreviations: CABG, coronary artery bypass graft; ESRD, end-stage renal disease; OHIP, Ontario Health Insurance Plan; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

4.2 Baseline Characteristics: General Population

The baseline characteristics of the matched general population (n=19,816) are presented in **Table 3**. The total follow-up time for the general population was 58,673 person-years. As expected, kidney transplant recipients had more co-morbidities than the general population, including coronary artery disease (31% vs. 4.9%), hypertension (74% vs. 20%), heart failure (14% vs. 1.1%), and diabetes mellitus (26% vs. 8.1%).

Table 3: Baseline characteristics of the matched general population in Ontario by era.

Characteristic	Total n=19,816	1994-1997 n=4192	1998-2001 n=4440	2002-2005 n=4728	2006-2009 n=6456	p value[a]
Age (years)	49 [38-59]	45 [35-55]	47 [36-57]	51 [41-60]	53 [42-62]	<0.001
Male	12,480 (63)	2656 (63)	2724 (61)	3036 (64)	4064 (63)	0.039
Income quintile[b]						
Lowest	3955 (20)	859 (20)	890 (20)	929 (20)	1277 (20)	
Middle	3846 (19)	837 (20)	839 (19)	899 (19)	1271 (20)	0.82
Highest	4139 (21)	835 (20)	920 (21)	1001 (21)	1383 (21)	
Urban residence[c]	17,444 (88)	3699 (88)	3922 (88)	4128 (87)	5695 (88)	0.41
Co-morbidities[d]						
Coronary artery disease	980 (4.9)	180 (4.3)	178 (4.0)	258 (5.5)	364 (5.6)	<0.001
Hypertension	3981 (20)	611 (15)	750 (17)	1038 (22)	1582 (25)	<0.001
Diabetes mellitus	1608 (8.1)	216 (5.2)	268 (6.0)	407 (8.6)	717 (11)	<0.001
Myocardial infarction	118 (0.6)	21 (0.5)	29 (0.7)	26 (0.5)	42 (0.7)	0.71
PCI	87 (0.4)	7 (0.2)	10 (0.2)	24 (0.5)	46 (0.7)	<0.001
CABG surgery	72 (0.4)	12 (0.3)	16 (0.4)	17 (0.4)	27 (0.4)	0.75
Heart failure	225 (1.1)	45 (1.1)	52 (1.2)	48 (1.0)	80 (1.2)	0.70
Stroke/TIA	57 (0.3)	14 (0.3)	9 (0.2)	15 (0.3)	19 (0.3)	0.66
Cardiovascular investigations[d]						
Holter monitor	610 (3.1)	106 (2.5)	96 (2.2)	149 (3.2)	259 (4.0)	<0.001
Echocardiography	1542 (7.8)	208 (5.0)	256 (5.8)	376 (8.0)	702 (11)	<0.001
Stress test	1675 (8.5)	246 (5.9)	294 (6.6)	438 (9.3)	697 (11)	<0.001
Coronary angiogram	264 (1.3)	37 (0.9)	42 (0.9)	68 (1.4)	117 (1.8)	<0.001
Carotid ultrasound	426 (2.1)	67 (1.6)	68 (1.5)	117 (2.5)	174 (2.7)	<0.001

Data presented as number (percentage) or median [interquartile range].

[a] Chi-square test for categorical variables and ANOVA for continuous variables (e.g. age).

[b] Income was categorized according to fifths of average neighborhood income, with the first quintile calculated as the lowest income and the fifth quintile as the highest income.

[c] Urban location indicates a population >10,000.

[d] Assessed by the presence of a diagnostic or procedural code in the 3 years prior to the transplant except for hypertension and diabetes mellitus which are defined as the presence of either 2 OHIP codes or 1 hospitalization with a diagnosis of hypertension or diabetes mellitus, respectively, in the 3 years prior to the transplant (an algorithm previously validated for hypertension and diabetes mellitus).(46,47)

Abbreviations: CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

4.3 Primary Outcome: Death or Major Cardiovascular Event

Kidney Transplant Recipients

The 3-year cumulative incidence and incidence rate of death or first major cardiovascular event for the entire cohort and for each era are presented in **Table 4**. There were a total of 445 composite outcome events (263 deaths and 182 major cardiovascular events, of which, 81 were myocardial infarctions) within the first 3 years following kidney transplantation (9.0%; 95% confidence interval [CI] 8.2% to 9.8%; 3.2 events per 100 person-years). The 3-year cumulative incidence of death or major cardiovascular event remained stable from 8.4% in 1994-1997 to 9.0% in 2006-2009 (p=0.41). When we adjusted for age, sex, and a history of coronary artery disease, myocardial infarction, hypertension, and diabetes mellitus, the risk of death or major cardiovascular event steadily declined across the eras (2006-2009 adjusted hazard ratio, aHR, 0.70; 95% CI 0.54 to 0.92; p=0.009; referent 1994-1997).

As expected, the highest incidence rate for each era was in the first 0-3 months after transplantation and steadily declined thereafter (**Table 5**). Overall, the incidence rate was 7.96 events per 100 person-years for the first 0-3 months following transplantation, 2.18 in the 4-12 months following transplantation, and 1.75 in the 13-36 months following transplantation. Among recipients who experienced an event, the time from transplantation to death or major cardiovascular event remained stable throughout the eras with a median time to event of 0.7 years (IQR 0.2 to 2.0) in 1994-1997 and 1.3 years (IQR 0.3 to 2.2) in 2006-2009.

Table 4: Death or major cardiovascular event[a] among kidney transplant recipients within 3 years following transplantation.

	Total n=4954	**1994-1997 n=1048**	**1998-2001 n=1110**	**2002-2005 n=1182**	**2006-2009 n=1614**	**p value[b]**
Number (%) of events	445 (9.0)	88 (8.4)	94 (8.5)	117 (9.9)	146 (9.0)	0.41
Number of events per 100 person-years	3.2	2.9	3.0	3.5	3.2	
Median time (years) to event [IQR]	1.2 [0.3-2.1]	0.7 [0.2-2.0]	1.3 [0.3-2.0]	1.4 [0.5-2.2]	1.3 [0.3-2.2]	
Number (%) of types of events[c]						
Death	263 (5.3)	51 (4.9)	49 (4.4)	79 (6.7)	84 (5.2)	0.33
Myocardial infarction	81 (1.6)	18 (1.7)	21 (1.9)	17 (1.4)	25 (1.5)	0.56
PCI or CABG surgery[d]	68 (1.4)	13 (1.2)	16 (1.4)	10 (0.8)	29 (1.8)	0.34
Ischemic stroke	33 (0.7)	6 (0.6)	8 (0.7)	11 (0.9)	8 (0.5)	0.83
Unadjusted hazard ratio (95% CI)	-	1.00 (Referent)	1.01 (0.75-1.35)	1.18 (0.90-1.56)	1.08 (0.83-1.40)	0.43
Adjusted hazard ratio[e] (95% CI)	-	1.00 (Referent)	0.89 (0.66-1.19)	0.83 (0.63-1.10)	0.70 (0.54-0.92)	0.009

[a] Major cardiovascular event was defined as either myocardial infarction, PCI, CABG surgery, or ischemic stroke.

[b] Cochran-Armitage test for trend except for hazard ratios for which Chi square was used..

[c] Only the first event is considered in this analysis.

[d] Due to the low number of events and for privacy reasons, the outcomes for PCI and CABG are reported in combination in this table.

[e] Adjusted for age, sex, and a history of coronary artery disease, myocardial infarction, hypertension, and diabetes mellitus at the time of transplantation.

Abbreviations: CABG, coronary artery bypass graft; CI, confidence interval; IQR, interquartile range; PCI, percutaneous coronary intervention.

Table 5: Incidence rate of death or major cardiovascular event[a] during 3 follow-up periods after kidney transplantation for recipients in each era.

Era	Incidence rate per 100 person-years (95% confidence interval)[b]		
	0-3 months	4-12 months	13-36 months
1994-1997 (n=1048)	8.60 (5.66 to 13.06)	2.67 (1.83 to 3.89)	1.32 (0.96 to 1.80)
1998-2001 (n=1110)	7.39 (4.77 to 11.46)	1.76 (1.12 to 2.75)	1.74 (1.34 to 2.27)
2002-2005 (n=1182)	6.59 (4.20 to 10.33)	2.43 (1.68 to 3.52)	2.10 (1.66 to 2.65)
2006-2009 (n=1614)	8.67 (6.20 to 12.14)	1.79 (1.23 to 2.59)	1.84 (1.48 to 2.27)
Overall	7.96 (6.53 to 9.70)	2.18 (1.80 to 2.63)	1.75 (1.55 to 1.99)

[a] Major cardiovascular event was defined as either myocardial infarction, PCI, CABG surgery, or ischemic stroke.

[b] Unadjusted Poisson model.

Abbreviations: CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention.

Subgroup Analysis

There was no difference in the primary outcome across the eras within age, sex, or donor type strata (**Figure 2**, **Figure 3**, and **Figure 4**, respectively). Throughout the study period, as expected a higher proportion of events were observed in the older population (19% for recipients ≥65 years old at the time of transplant vs. 7.6% for recipients <65 years; p<0.001), in males vs. females (9.6% vs. 7.9%; p=0.04), and in recipients of deceased donor kidneys vs. living donor kidneys (11% vs. 5.5%; p<0.001).

Figure 2: 3-year cumulative incidence of death or major cardiovascular event from 1994 to 2009 stratified by age.

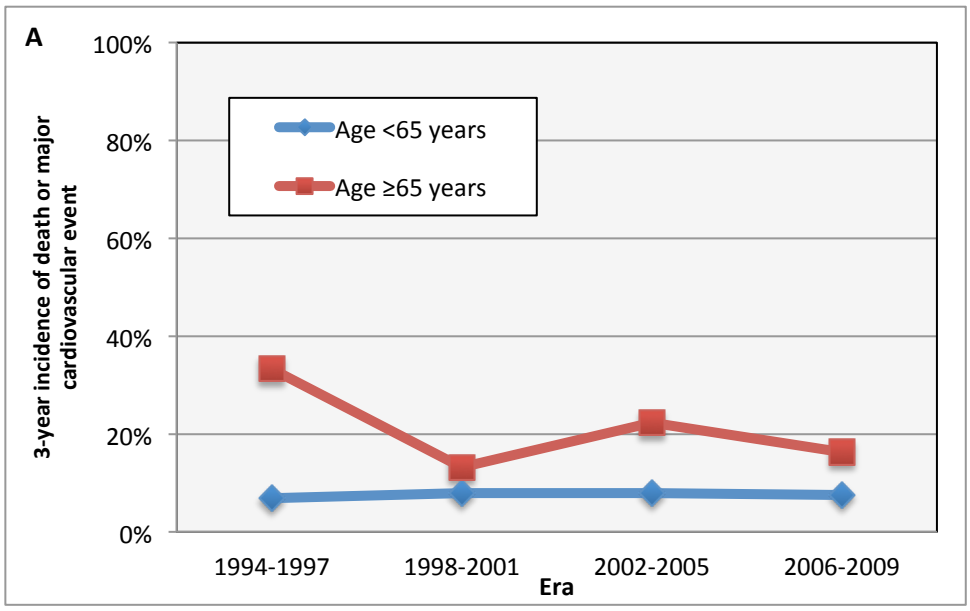


Figure 3: 3-year cumulative incidence of death or major cardiovascular event from 1994 to 2009 stratified by sex.

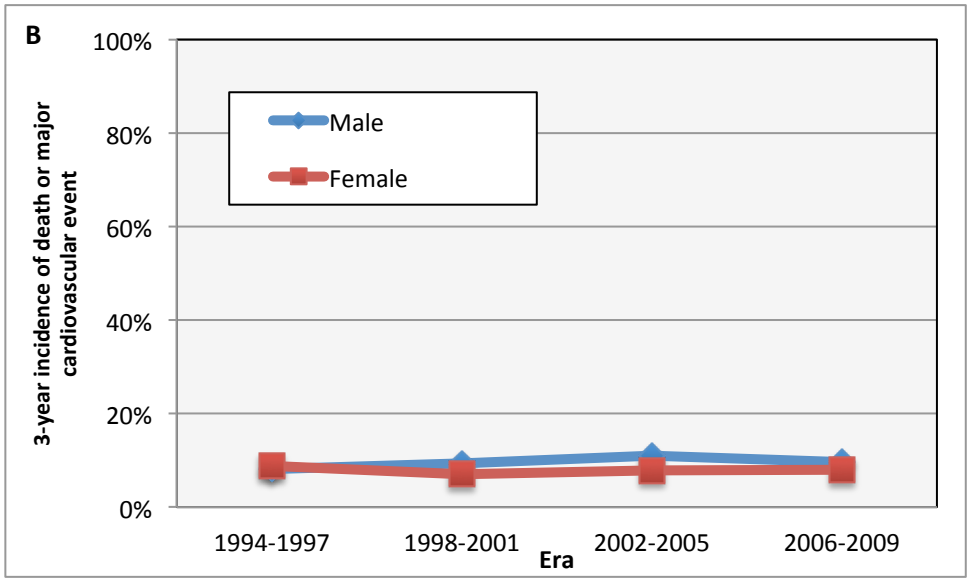
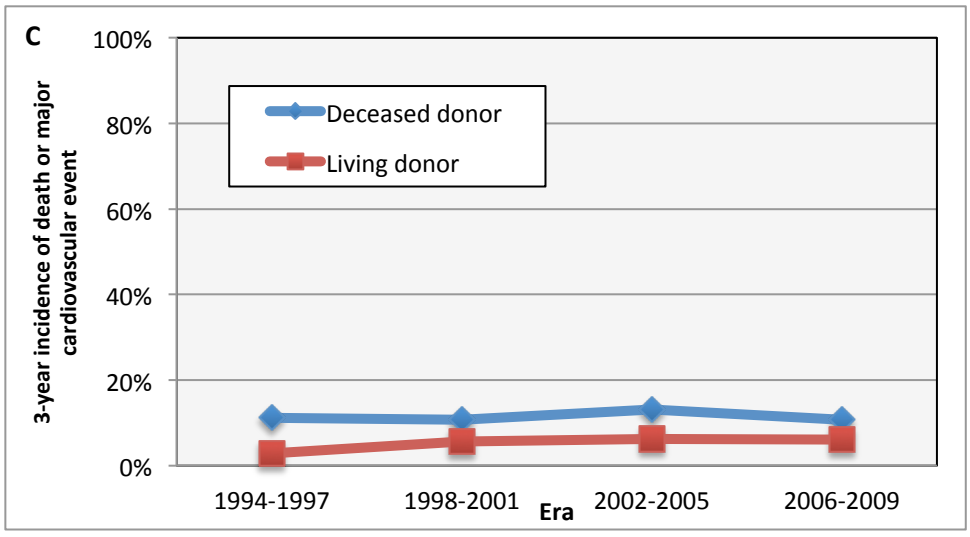


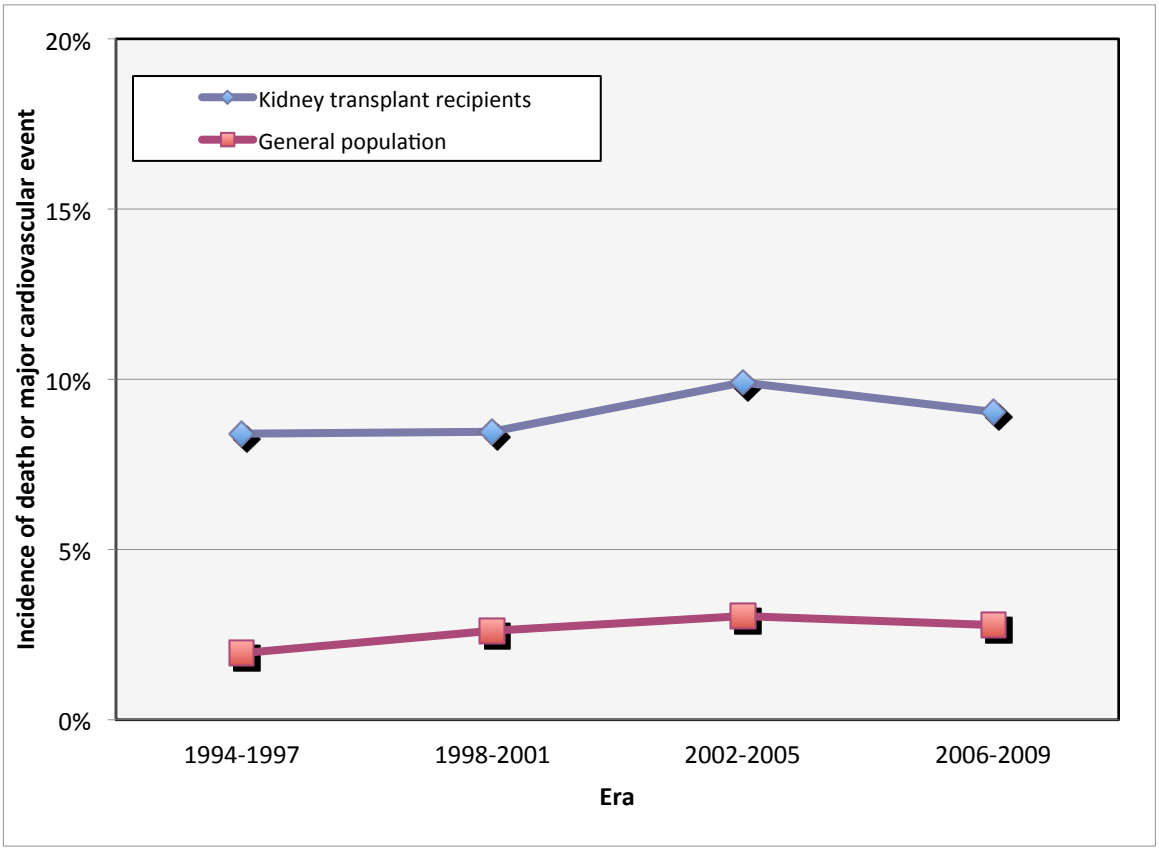
Figure 4: 3-year cumulative incidence of death or major cardiovascular event from 1994 to 2009 stratified by donor type.



Comparison to the General Population

A comparison of the primary outcome in kidney transplant recipients to the general population (matched on age, sex, and index date) is presented in **Figure 5**. Overall, the 3-year cumulative incidence and rate of death or first major cardiovascular event was lower in the general population (2.6%; 95% CI 2.4% to 2.9%; 0.89 events per 100 person-years; p<0.001) compared to recipients, with a trend towards increasing incidence over time (2.0% in 1994-1997 to 2.8% in 2006-2009; p=0.008).

Figure 5: 3-year cumulative incidence of death or major cardiovascular event from 1994 to 2009 in matched kidney transplant recipients and general population. The general population cohort excluded individuals with chronic kidney disease, a history of dialysis or previous kidney transplantation. Kidney transplant recipients were matched 1:4 to members of the general population based on age, sex, and index date.



4.4 Additional Outcome: Death

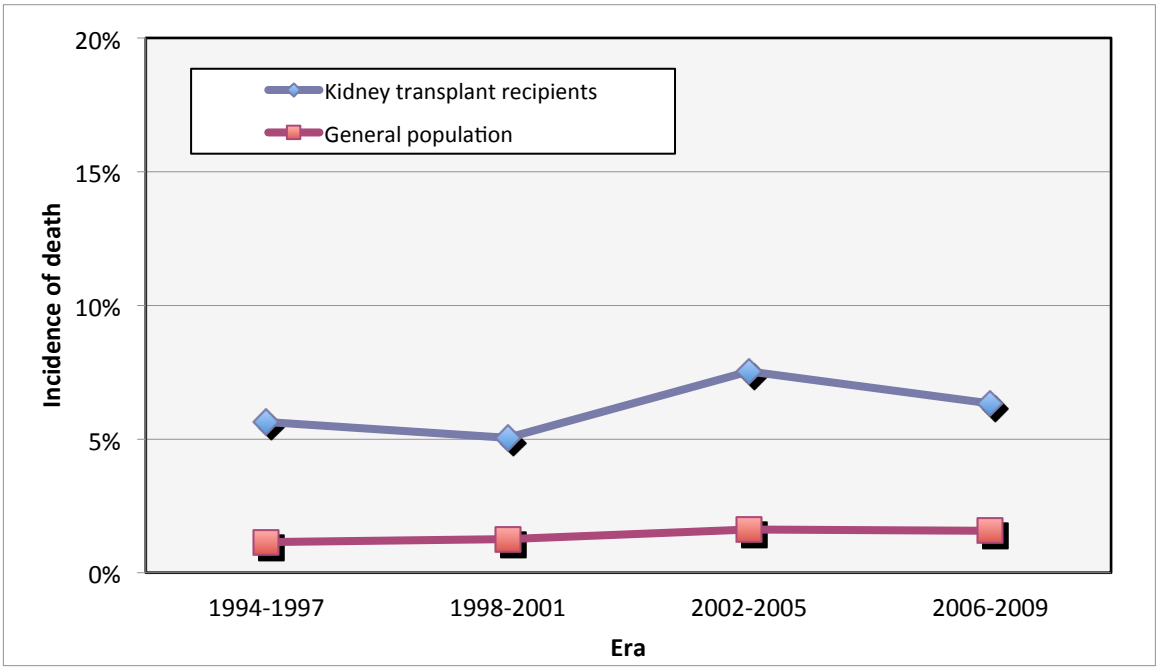
The components of the primary outcome were examined separately. There were 306 deaths within 3 years following transplantation (6.2%; 95% CI 5.5% to 6.9%; 2.1 events per 100 person-years) with no difference across the eras (5.6% in 1994-1997 vs. 6.3% in 2006-2009; p=0.17) (**Table 6**). The 3-year cumulative incidence and rate of death was lower in the general population (1.4%; 95% CI 1.3% to 1.6%; 0.5 events per 100 person-years; p<0.001) compared to recipients, with a trend towards increasing incidence over time (p=0.017) (**Figure 6**).

Table 6: Secondary outcomes of 3-year cumulative incidence of death, cardiovascular events, and cardiovascular investigations among kidney transplant recipients.

Number (%) of events	**Total n=4954**	**1994-1997 n=1048**	**1998-2001 n=1110**	**2002-2005 n=1182**	**2006-2009 n=1614**	**p value**[a]
Death	306 (6.2)	59 (5.6)	56 (5.0)	89 (7.5)	102 (6.3)	0.17
Cardiovascular events (censored for death)[b]						
Major cardiovascular event[c]	182 (3.7)	37 (3.5)	45 (4.1)	38 (3.2)	62 (3.8)	0.92
Myocardial infarction	81 (1.6)	18 (1.7)	21 (1.9)	17 (1.4)	25 (1.5)	0.56
PCI	67 (1.4)	12 (1.1)	15 (1.4)	11 (0.9)	29 (1.8)	0.21
Ischemic stroke	36 (0.7)	8 (0.8)	8 (0.7)	11 (0.9)	9 (0.6)	0.61
Cardiovascular investigations						
Holter monitor	395 (8.0)	64 (6.1)	82 (7.4)	80 (6.8)	169 (11)	<0.001
Echocardiography	1898 (38)	305 (29)	359 (32)	450 (38)	784 (49)	<0.001
Stress test	1133 (23)	204 (19)	222 (20)	269 (23)	438 (27)	<0.001
Coronary angiogram	81 (1.6)	10 (1.0)	17 (1.5)	16 (1.4)	38 (2.4)	0.008
Carotid ultrasound	366 (7.4)	74 (7.1)	84 (7.6)	73 (6.2)	135 (8.4)	0.32

[a] Cochran-Armitage test for trend.
[b] Due to the low number of events and for privacy reasons, the outcomes for CABG are not reported in this table. The total number of events was 42 (0.8%) with no significant change over time (p=0.63).
[c] Major cardiovascular event was defined as either myocardial infarction, PCI, CABG surgery, or ischemic stroke.
Abbreviations: CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention.

Figure 6: 3-year cumulative incidence of death from 1994 to 2009 in matched kidney transplant recipients and general population. The general population cohort excluded individuals with chronic kidney disease, a history of dialysis or previous kidney transplantation. Kidney transplant recipients were matched 1:4 to members of the general population based on age, sex, and index date.



4.5 Additional Outcome: Death-Censored Major Cardiovascular Events

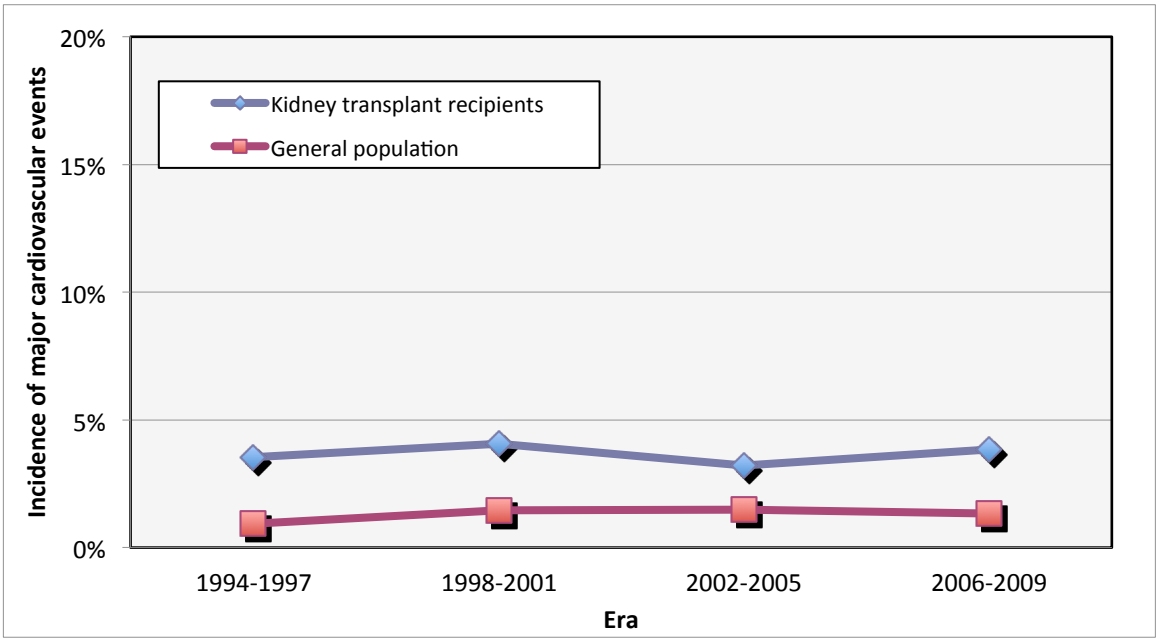
In kidney transplant recipients, there was no significant change in the 3-year cumulative incidence of death-censored major cardiovascular events (182 events; 3.7%; 95% CI 3.2% to 4.2%; 1.2 events per 100 person-years) across the eras (3.5% in 1994-1997 vs. 3.8% in 2006-2009; p=0.92) (**Table 6**). The 3-year incidence of death-censored major cardiovascular event was lower in the general population (1.3%; 95% CI 1.2% to 1.5%; 0.4 events per 100 person-years; p<0.001) compared to recipients, with no significant change over time in either group (p=0.14) (**Figure 7**).

In kidney transplant recipients, the 3-year cumulative incidence of myocardial infarction was 1.7% in 1994-1997 compared to 1.5% in 2006-2009 (p=0.56) (**Table 6**). When examined separately, the 3-year cumulative incidences of percutaneous coronary intervention, coronary artery bypass graft surgery, and ischemic stroke also remained stable throughout the eras.

There was a trend towards more cardiac investigations (Holter monitor, echocardiography, stress testing, coronary angiogram) in the 3-years following kidney transplantation in the more recent eras (**Table 6**). The use of carotid ultrasounds remained stable throughout the eras.

Lastly, in the post-operative transplant period, the 30-day cumulative incidence of myocardial infarction was 1.5% while the 30-day cumulative incidence of ischemic stroke was 0.3%.

Figure 7: 3-year cumulative incidence of death-censored major cardiovascular event from 1994 to 2009 in matched kidney transplant recipients and general population. The general population cohort excluded individuals with chronic kidney disease, a history of dialysis or previous kidney transplantation. Kidney transplant recipients were matched 1:4 to members of the general population based on age, sex, and index date.



Chapter 5 : Discussion

5.1 Summary of Key Findings

In this study, we found that the 3-year cumulative incidence of death or major cardiovascular event in kidney transplant recipients was 9.0% and, reassuringly, has remained stable over time despite increasing recipient age and co-morbidities in the more recent eras. When we adjusted for age, sex, and baseline co-morbidities, there was a trend towards a decreasing risk of death or major cardiovascular event across the eras.

The incidence rate was highest in the first 3 months after transplantation and steadily declined thereafter. There was no difference in the primary outcome when the results were stratified by age, sex, and donor type. Compared to the general population, kidney transplant recipients have a higher incidence of death or major cardiovascular event.

Similar results were seen when the components of the primary outcome were examined separately. The 3-year cumulative incidence of death in kidney transplant recipients was 6.2% and for death-censored major cardiovascular event was 3.7%, with no significant change over time for either outcome. The 3-year cumulative incidence of myocardial infarction was 1.6% and for ischemic stroke was 0.7% with no significant change over time.

5.2 Comparison of Results to Previous Research

Similar to an Australian study, we found a trend towards a greater proportion of older recipients with more co-morbidities in recent years.(8) This trend may be due to the increasing rate of treated end-stage renal disease (ESRD) among the elderly (over a third are now >70 years old).(48,49) While younger recipients do have higher patient and graft survival rates compared to older recipients,(49) studies have shown that older patients still have a survival benefit with kidney transplantation compared to remaining on

dialysis and that death-censored graft survival is similar to younger recipients.(1,50–53) This raises ethical dilemmas in the allocation of scarce resources and a growing number of patients on the transplant waiting list.(54,55) Of note, the United States (U.S.) recently implemented a revised deceased donor allocation policy in December 2014 which prioritizes kidney transplant candidates with the highest expected post-transplant survival (a metric based on age, diabetes mellitus, dialysis time, and prior transplant status) for the highest quality organs.(56) Despite the favourable outcomes with transplantation for older patients on the waiting list, there are concerns regarding this population's higher risk of death with a functioning graft as well as post-transplant complications including cardiovascular events.(54) Reassuringly, we found that the 3-year cumulative incidence of death or major cardiovascular event in this older age group has remained stable.

The overall 3-year cumulative incidence of death or major cardiovascular event was 9.0% in our cohort while the 3-year cumulative incidence of myocardial infarction and ischemic stroke were 1.6% and 0.7%, respectively. These estimates are lower than the 11% and 3.5% 3-year cumulative incidence of myocardial infarction and ischemic stroke reported in Lentine's *et al*. retrospective studies of Medicare-insured kidney transplant recipients followed through the United States Renal Data System (USRDS).(7,57) The higher cumulative incidence of myocardial infarction in the U.S. study compared to our Canadian study may be due to differences in baseline characteristics between the two cohorts and/or how myocardial infarction events were captured. The U.S. cohort had a higher proportion of older recipients (22% of U.S. recipients were ≥60 years compared to 12% of our recipients were ≥65 years) and a higher proportion of recipients for whom diabetes mellitus was the primary cause of ESRD (25% vs. 18%). The U.S. cohort also had a higher proportion of recipients with concurrent co-morbidities at the time of transplant. For example, 45% of U.S. recipients had diabetes mellitus vs. 26% of our recipients and 8% of U.S. recipients had a history of myocardial infarction pre-transplant compared to 2% of our cohort. However, baseline co-morbidities may be under-represented in our cohort given that they only reflect recorded diagnostic and procedural codes present in the 3 years prior to transplantation. In addition, we restricted our events to hospitalizations within 3 years of transplantation

where the most responsible diagnosis was myocardial infarction whereas the U.S. study included any Medicare billing claims within 3 years of transplantation with a diagnosis of myocardial infarction or death due to myocardial infarction. A previous validation study has shown that a most responsible diagnosis of acute myocardial infarction has a specificity, sensitivity, and positive predictive value of 93%, 89%, and 89%, respectively. Thus, myocardial infarctions or strokes occurring in the immediate peri-operative period are unlikely to be captured in our primary analysis, as the most responsible diagnosis related to the admission would likely be the kidney transplantation rather than complications arising post-operatively.

Regarding peri-operative events, in our secondary analysis we did not limit the hospital diagnostic code to most responsible or primary diagnosis and found that the 30-day cumulative incidence of myocardial infarction was 1.5% while the 30-day cumulative incidence of ischemic stroke was 0.3%. This is similar to a previous retrospective single-center study by Humar *et al.* who found that in a cohort of 2694 kidney transplant recipients the 30-day incidence of myocardial infarction was 1.6%.(58) We did confirm that the highest incidence rate of death or major cardiovascular event occurred during the first 0-3 months after transplantation (7.96 events per 100 person-years in the first 0-3 months vs. 2.18 events per 100 person-years in the 4-12 months vs. 1.75 events per 100 person-years in the 12-36 months).

5.3 Further Discussion of Results

There are many possible reasons for the stable rate of observed events in our cohort despite the changing baseline characteristics of our recipients. One reason may be the increase in living donor kidneys over time for which these recipients, in our study, were found to have a lower risk of death or cardiovascular event compared to deceased donor kidney recipients (overall, 5.5% for living donor kidneys vs. 11% for deceased donor kidneys). Another possible reason may be the careful assessment and selection process of kidney transplant candidates. In recent years, we noted a dramatic increase in the proportion of recipients who received cardiac investigations in the 3 years prior to their transplant, likely as part of their transplant assessment and/or cardiac surveillance while on the transplant waiting list. A survey of transplant programs in the U.S. showed wide variability in the use of invasive and non-invasive cardiac investigations used as part of the screening and surveillance of potential kidney transplant candidates.(59) Among Medicare-insured transplant recipients in the U.S. between 1991 and 2004, 46% (65% of high-risk and 20% of lower-risk patients) underwent cardiac evaluation testing before transplantation.(60) Kidney transplant recipients who were younger, female, African-American, or had a shorter duration on dialysis were less likely to undergo pre-transplant cardiac evaluation with non-invasive stress testing and angiography.

Although there are recommendations on the cardiac evaluation and surveillance of potential transplant recipients, these tests have been inconsistent in predicting or mitigating post-transplant cardiovascular mortality or morbidity.(6) A Cochrane review of cardiac testing for coronary artery disease in kidney transplant candidates suggested that dobutamine stress echocardiography is the screening investigation of choice but recognized the limitation of cardiac testing in predicting cardiac event-free survival after transplantation.(61) Similarly, a Canadian prospective study from British Columbia of 604 patients on the kidney transplant waiting list between 1998 and 2001 found that the use of non-invasive cardiac investigation prior to transplant was not predictive of the time to a cardiovascular event post-transplant.(62) In our study, we cannot attribute the stability of post-transplantation cardiovascular events to the increase in cardiac testing pre-transplantation. Currently there is no evidence from randomized trials demonstrating

that pre-operative cardiac screening of asymptomatic patients reduces risk of major cardiovascular events or improves survival after transplantation or other forms of surgery.(6)

Finally, progressive improvements in the diagnosis and medical management of cardiovascular events in patients with chronic kidney disease (CKD) may explain our findings.(29,63–65) As above, there is a lack of randomized controlled trials proving efficacy of pharmacological interventions in the reduction of cardiovascular events in patients with renal disease as these patients are often excluded from the trials.(66) Thus, physicians often extrapolate findings from the general population to the CKD population despite their unique cardiac risk factors and pathophysiology.(29) Unfortunately, we did not have complete information on cardio-protective medications, such as beta-blockers or statins, in our data sources given that a significant proportion of recipients are covered by private drug plans.

Despite the stable cumulative incidence of cardiovascular events over time, kidney transplant recipients had a 6.4% higher risk of death or major cardiovascular event compared to the general population. As previously stated, this is likely due to the combination of traditional cardiovascular risk factors and renal-specific cardiovascular risk factors that are highly prevalent in this unique patient population.(21,23) Traditional cardiovascular risk factors include hypertension, diabetes mellitus, hyperlipidemia, smoking, older age, and physical inactivity. Renal-specific factors include decreased renal function (compared to the general population), immunosuppressive medications, episodes of rejection and graft loss, and donor type (living vs. deceased donors).(20,23,24) In our subgroup analyses, the risk of death or major cardiovascular event was higher in kidney transplant recipients who were older and had received kidneys from deceased donors.

5.4 Study Strengths

Our study has a number of strengths. To our knowledge, this is the first study assessing secular trends of death and major cardiovascular events in kidney transplant recipients. Our study was made possible because of Ontario's universal healthcare benefits, with the collection of all healthcare encounters for all citizens, including almost 5000 transplant recipients followed in this study. This minimizes concerns about selection and information biases. We relied on diagnostic and procedural codes for our outcomes with proven validity compared to chart review.

5.5 Study Limitations

There are some limitations to our study. We did not have accurate and complete data to compare our results to a population of patients receiving chronic dialysis while on the transplant waiting list. Cause of death could not be accurately obtained in our data sources. We relied on administrative data collected for non-research purposes, which limit the type of data available for applying inclusion/exclusion criteria as well as for outcome measurements. Claims are surrogate measures for diagnoses and procedures, but have been shown to have high sensitivity and specificity compared with chart review and registry data in the general Ontario population (**Appendix 3**). High sensitivity of Medicare billing claims for cardiovascular diagnoses and procedures in the kidney transplant population has also been demonstrated in the U.S.(67) Residual confounding, inherent to any observational study, may affect the association between year of transplant and outcomes. Historical information such as smoking, cardio-protective medications, immunosuppression use, physical exam values such as blood pressure measurements, laboratory data such as serum creatinine or cardiac troponin, and investigational findings such as echocardiography results were unavailable or incomplete from our data sources. Lastly, secular changes in coding practices or outcome definitions may have influenced our results although most codes have remained stable over time.

5.6 Conclusion

We report a stable cumulative incidence over time of post-transplant death or major cardiovascular event in kidney transplant recipients despite increasing recipient age and co-morbidities. Our results are reassuring for transplant programs and may reflect advances in the prevention and treatment of cardiovascular disease in kidney transplant recipients.

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Appendices

Appendix 1: Data creation plan.

Secular Trends in Cardiovascular Disease Among Kidney Transplant Recipients

Number of Study	2014 0906 032 000
Research Program	Kidney, Dialysis, & Transplantation (KDT)
Contacts	Ngan N. Lam Amit X. Garg S. Joseph Kim Greg A. Knoll Salimah Z. Shariff Kyla L. Naylor Eric McArthur Alvin H. Li
Responsible for Updates	Ngan Lam
PIA Approved?	Yes (April 15, 2013)
DCP update history	Version 11: February 5, 2015 (NL, after receiving co-author comments) Version 10: November 3, 2014 (NL, after drafting manuscript) Version 9: July 6, 2014 (NL, after updating variable library) Version 8: May 4, 2014 (NL, after reviewing DCP again) Version 7: December 28, 2013 (NL, after receiving results) Version 6: June 13, 2013 (NL, after receiving Table 1) Version 5: June 3, 2013 (NL, after call with JK/GK and meeting with EM/SD) Version 4: May 15, 2013 (NL, after meeting with entire group) Version 3: May 3, 2013 (NL, after emailing group, meeting with SM and KN) Version 2: April 14, 2013 (NL, after meeting with JF and SD) Version 1: March 29, 2013 (NL, after meeting with AG) Version 0: March 12, 2013 (NL)
Short Description of Research Question	Our aim is to assess whether rates and outcomes of major adverse cardiovascular events (MACE) in kidney transplant recipients have changed over time in Ontario, Canada from 1994 to 2009. Specifically, we will assess incidence and temporal (annual) trends of major adverse cardiovascular events after kidney transplantation. We will compare these incidences to the general population.
List of Datasets Used	1. CORR (Jan 1981 – Dec 2012) 2. RPDB (Jan 1991 – Dec 2012) 3. CIHI-DAD (Jan 1991 – Dec 2012) Source ☒ All Institution types ☒ Acute care (insttype = 'AP' or 'AT') Diagnosis Type (dxtype) ☒ All (alldx) (for baseline characteristics) ☒ Most responsible diagnosis (M) (for cardiovascular outcomes) Study period ☒ Prior to 2002 fiscal year → INCLUDE ICD-9 CODES in **Appendix A, B, E** ☒ From 2002 fiscal year and onwards → INCLUDE ICD-10 CODES in **Appendix A, B, E** Include suspected/questionable diagnoses? ☒ No

	Reference date ☒ Do include index date in look-forward period (start at index) Include abandoned procedures? ☒ No 4. OHIP (July 1991 – Dec 2012) Claim Type ☒ Non-lab claims Code Types ☒ Feecodes → INCLUDE FEECODES in **Appendix A, B, E** ☒ Diagnosis codes → INCLUDE DIAGNOSIS CODES in **Appendix A, B, E**

Design: Retrospective Cohort Study

Defining the Cohort

Index Event

Year of first kidney-only transplantation (from a deceased or living donor) during the study period (1994 to 2009) using CORR as the data source for kidney transplant recipients.

Inclusion Criteria (Table 1a, Table 1b, Table 1c)

1) Cohort A: Kidney transplant recipients (KTx)
All incident kidney-only transplant recipients in Ontario from **January 1, 1994** to **December 31, 2009** with a valid IKN.
CORR Dataset: RECIPIENT_TREATMENT
- Variable: TREATMENT_CODE = 171 (Acute Care Hospital, Transplantation, Total Care)
- Variable: TREATMENT_DATE (date of transplant)
- Variable: TRANSPLANTED_ORGAN_TYPE_CODE[1-3]

CORR: TRANSPLANTED_ORGAN_TYPE_CODE[1-3]	Code
Kidneys/Dialysis (includes enbloc transplants)	10
Kidney – Left	11
Kidney – Right	12
Kidney – One (from conversion)	18
Kidney – Two (from conversion)	19

2) Cohort B: General population (GP)
Restrict to those in RPDB. Randomly assign an index date (from **January 1, 1994** to **December 31, 2009**) to all based on the distribution of the index dates in the kidney transplant recipients above (minimum, maximum, 25th, 50th, 75th percentiles).

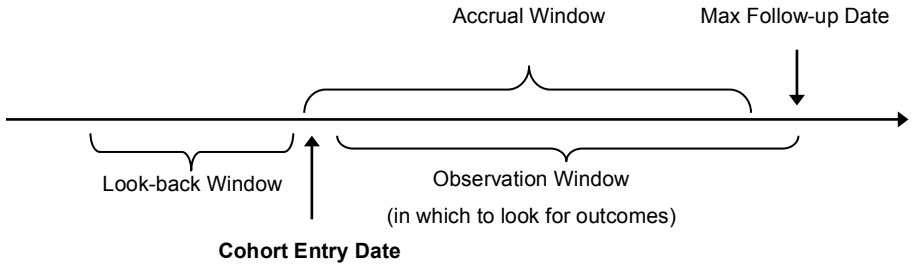
Exclusions (In order) (Table 1)

Data cleaning steps (both cohorts)
1. Exclude if invalid or missing IKN, date of birth, or sex
2. Death before the index date in RPDB
3. Exclude non-Ontario residents (use the "%getdemo" macro, the "prcddablk" variable, exclude recipients whose province code, pr, is not "35")

Further exclusions (4 to 5a-c are both cohorts)
4. Exclude if age <18 at index date (RPDB)
5. Look back from the index date to 1981 for CORR or 1991 for CIHI-DAD/OHIP for the following:
a. Exclude if repeat/previous kidney transplant or history of non-kidney transplant.
CORR Dataset: RECIPIENT_TREATMENT
- Variable: TREATMENT_CODE = 171 or 181
For Cohort A (KTx), only include first transplant event, not re-transplants; i.e. first 171 for a given patient. Index transplant should be the first transplant only.
b. Exclude if CORR reports graft number ≥2
CORR Dataset: TRANSPLANTED_KIDNEY
- Variable: GRAFT_NUM ≥2
For Cohort A (KTx), should be 1 for all recipients.

	c. Exclude if evidence of CIHI-DAD or OHIP codes for kidney transplant (**Appendix A**) from beginning of available databases to -60 days before index date Cohort A (KTx) only 6. Exclude if simultaneous multi-organ transplant recipient including kidney-pancreas CORR Dataset: RECIPIENT_TREATMENT - Variable: TRANSPLANTED_ORGAN_TYPE_CODE[1-3] as above (in inclusion #1) Cohort B (GP) only 6. Look back from the index date to 1981 for CORR or 1991 for CIHI-DAD/OHIP for the following: a) Exclude if evidence of chronic dialysis in CORR. CORR Dataset: RECIPIENT_TREATMENT (Dialysis codes in **Appendix D**) b) Exclude if evidence of CIHI-DAD or OHIP codes for dialysis (**Appendix A**) before the index date 7. Exclude if evidence of CIHI-DAD code for CKD before the index date (look back to 1991) (CKD codes in **Appendix D**).
Matching	Match up to 4 controls (Cohort B [GP]) to each recipient (Cohort A [KTx]) on the following characteristics: i) Index date (± 6 months; when possible, ensure control has the same index year as the recipient) ii) Age at index date (± 1 year) iii) Sex
Size of Cohort	Based on previous analyses, we anticipate that between 1994 to 2009, there will be approximately 5000 incident kidney-only transplant recipients (from living or deceased donors) eligible for inclusion into the study cohort.

Time Frame Definitions



Accrual Start/End Dates	Start: January 1, 1994 End: December 31, 2009
Max Follow-up Date	December 31, 2012
When Does Observation Window Terminate?	Termination occurs (whichever comes first): 1. Observed outcome/event (see **Outcome Definitions** section) 2. End of follow-up (either pre-defined follow-up period of 30 days, 3 years, 5 years, or 10 years based on outcome) or end of study period (Dec 31, 2012) 3. Death
Look-back Window(s)	3 years prior to index date for co-morbid conditions (earliest potential date is January 1, 1991)

Variable Definitions

Main Exposure or Risk Factor

Year of kidney-only transplantation from either a living or deceased donor.
CORR Dataset: RECIPIENT_TREATMENT
- Variable: TREATMENT_DATE (year of transplant)

Baseline Characteristics (Table 2a, Table 2b, Table 2c) (Appendix B)

Note: There will be a separate cohort for each accrual era (era that patient is put into depends on when the patient has their transplant: 1994-1997, 1998-2001, 2002-2005, 2006-2009). Therefore, there will be 4 consecutive cohorts for the primary outcome.

Observed at the time of the index date – Demographics (CORR, RPDB) (Table 2):

Record mean (with standard deviation), median (with interquartile range), minimum, maximum, and/or categorical number N(%) for the following variables as indicated for all 3 cohorts except where indicated:

1. Age at index date: Years, mean±SD, median (IQR), minimum, maximum; Categories: ≤44 years, 45-64 years, ≥65 years, N(%) (RPDB)
2. Sex: Female, Male, N(%) (RPDB)
3. Race (Cohort A [KTx] only): Categories: Caucasian (White), Asian, Black, Indian Subcontinent, Other, Unknown/Missing, N(%)
CORR Dataset: RECIPIENT
- Variable: RACIAL_ORIGIN_CODE
Look back to the beginning of CORR (1981) to find race.

CORR: RACIAL_ORIGIN_CODE	Examples	Codes
Caucasian (White)	French Canadians, European, Australian, Russian ancestry	01
Asian	Chinese, Japanese, Vietnamese, Korean, Taiwanese	02
Black	African, Jamaican, Haitian, Somali	03
Indian Subcontinent	Indian, Pakistani, Bangladesh	05
Other	Filipino Aboriginal (North American Indian, Metis, Inuit) Middle Eastern/Arabian (Saudi Arabian, Iranian, Iraqi, Jordanian, Syrian, Armenian, Algerian) Latin American (Caribbean, South American, Cuban) Other/Multiracial	08 09 10 11 99
Unknown	Unknown	98

4. Income quintile: Quintile 1-5, Missing, N(%) (PCCF, use PSTLYEAR data and index year)
5. Rural location: Rural, Urban, Missing, N(%)

Observed at the time of the index date – Kidney-related factors (CORR) (Table 2):

Record categorical number (%) for the following variables (Cohort A [KTx] only):

1. Index date: N(%); Categories/Eras: 1994-1997, 1998-2001, 2002-2005, 2006-2009
CORR Dataset: RECIPIENT_TREATMENT
- Variable: TREATMENT_CODE = 171
- Variable: TREATMENT_DATE
- Variable: TRANSPLANTED_ORGAN_TYPE_CODE[1-3] (see table in **Inclusion Criteria**)

2. Primary cause of end-stage renal disease: Glomerulonephritis/Autoimmune, Cystic Kidney Disease, Diabetes, Renal Vascular Disease, Other, Unknown/Missing, N(%) (**Appendix C**)
CORR Dataset: RECIPIENT_TREATMENT

- Variable: PRIMARY_DIAGNOSIS_KIDNEY
Look back to the beginning of CORR (1981) to find primary cause of ESRD.

3. Dialysis modality: Hemodialysis, Peritoneal Dialysis, Other, Pre-emptive/Missing, N(%) (**Appendix D**)
CORR Dataset: RECIPIENT_TREATMENT
- Variable: TREATMENT_CODE
Note: For patients with Missing dialysis modality (assumed to be pre-emptive recipients), look back for evidence of chronic dialysis codes and re-classify these patients as HD or PD (see codes in **Appendix B**). For duplicate codes (G333, H540, H740), classify as HD.

4. Donor type: Living, Deceased, Unknown/Missing, N(%)
CORR Dataset: TRANSPLANTED_KIDNEY
- Variable: DONOR_TYPE_CODE

Donor type	CORR: DONOR_TYPE_CODE	Code
Living	Parent	02
	Sibling	03
	Offspring	04
	Other relative	05
	Other living unrelated	06
	Spouse	07
	Anonymous/altruistic	10
	Domino donor	12
	Paired	15
Deceased	Deceased donor	01
Unknown	Unknown/Out-of-country transplant	98

Observed in the first 60 days of the index date – Kidney-related factors (CIHI-DAD, OHIP) (Table 2):

Record categorical number (%) for the following variables (Cohort A [KTx] only):

1. Delayed graft function: At least one code for dialysis appearing in the first 7 days after the index date (see **Appendix B** for dialysis codes), N(%)

2. Primary renal allograft non-function: At least three codes for dialysis on three different days with at least one code appearing in the first 7 days after the index date, in the 8-30 days after the index date, and in the 31-60 days after the index date (see **Appendix B** for dialysis codes), N(%)

Look back 3 years from index date (CIHI-DAD, OHIP) (Table 2):

CIHI-DAD
Diagnosis Type (dxtype)
☒ All (alldx)

Record categorical number (%) for the following variables unless otherwise stated for all 3 cohorts:

Co-morbidities:
1. Coronary artery disease (CAD) without angina (CIHI-DAD, OHIP)
2. Myocardial infarction (CIHI-DAD)
3. Percutaneous coronary intervention (PCI) (CIHI-DAD, OHIP)
4. Coronary artery bypass graft (CABG) surgery (CIHI-DAD, OHIP)

	5. Heart failure (CIHI-DAD, OHIP) 6. Hypertension (CIHI-DAD, OHIP): Define as evidence of two OHIP claims for hypertension OR one hospitalization with a diagnosis of hypertension within the three-year look-back window 7. Diabetes (CIHI-DAD, OHIP): Define as evidence of two OHIP claims for diabetes OR one hospitalization with a diagnosis of diabetes within the three-year look-back window 8. Stroke/TIA (CIHI-DAD) Cardiac testing (a recipient can have ≥1 test/visit in the 3-year look-back window): 1. Carotid ultrasound (CIHI-DAD, OHIP) 2. Coronary angiogram (CIHI-DAD, OHIP) 3. Echocardiography (CIHI-DAD, OHIP) 4. Holter monitoring (CIHI-DAD, OHIP) 5. Stress test (CIHI-DAD, OHIP) **Variable look-back window (CORR) (Table 2):** Record mean (with standard deviation), median (with interquartile range), minimum, maximum, and/or categorical number (%) for the following variables as indicated (Cohort A [KTx] only): 1. Time on dialysis prior to transplantation date: Years, mean±SD, median (IQR), minimum, maximum. CORR Dataset: RECIPIENT_TREATMENT - Variable: TREATMENT_DATE ≠171 for first date - If 171 is the first date, then assume pre-emptive transplant (i.e. Years on dialysis = 0) - Calculation: Time on dialysis (years) = ([Treatment_Date] & [Treatment_Code] “171”) – ([Treatment Date] & [Treatment Code] “Dialysis Codes in **Appendix D**”)
Outcome Definitions (Table 3a, Table 3b, Table 3c) (Appendix E)	**Outcomes** CIHI-DAD (Jan 1991 – Dec 2012) <u>Source</u> ☒ All <u>Institution types</u> ☒ Acute care (insttype = ‘AP’ or ‘AT’) <u>Diagnosis Type (dxtype)</u> ☒ Most responsible diagnosis (M) ☒ All (alldx) (for 30-day outcomes) <u>Study period</u> ☒ Prior to 2002 fiscal year → INCLUDE ICD-9 CODES in **Appendix E** ☒ From 2002 fiscal year and onwards → INCLUDE ICD-10 CODES in **Appendix E** <u>Include suspected/questionable diagnoses?</u> ☒ No <u>Reference date</u> ☒ Do include index date in look-forward period (start at index) <u>Include abandoned procedures?</u> ☒ No OHIP (July 1991 – Dec 2012) <u>Claim Type</u> ☒ Non-lab claims <u>Code Types</u> ☒ Feecodes → INCLUDE FEECODES in **Appendix E** ☒ Diagnosis codes → INCLUDE DIAGNOSIS CODES in **Appendix E**

Primary outcome (CIHI-DAD, OHIP) (Table 3a):

1. Composite of death or first major adverse cardiovascular event (MACE) within 3 years of index date (myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, ischemic stroke). Use codes defined in **Appendix E**
For each cohort era, report the number of events that occurred in the follow-up period within that cohort (i.e. not the number of events that occurred that era. For example, a new kidney-only transplant recipient receives their transplant in 1995 and enters the 1994-1997 cohort. If this patient has a stroke in 1998, then the cardiovascular event is reported in the 3-year outcomes of the 1994-1997 cohort.)

Secondary outcomes at 3 years (CIHI-DAD, OHIP) (Table 3b):

1. Death within 3 years of index date

2. First major adverse cardiovascular event within 3 years of index date censored for death

3. Major adverse cardiovascular event by type within 3 years of index date (censor for death):
Here, the denominator is the total number of recipients in each cohort era
i) Myocardial infarction
ii) Percutaneous coronary intervention
iii) Coronary artery bypass graft surgery
iv) Ischemic stroke

4. Cardiac testing by type within 3 years of index date:
i) Carotid ultrasound
ii) Coronary angiogram
iii) Echocardiography
iv) Holter monitoring
v) Stress test

Secondary outcomes at 30 days (CIHI-DAD, OHIP) (Table 3c):
CIHI-DAD
Diagnosis Type (dxtype)
☒ All (alldx)

5. 30-day cumulative incidence of myocardial infarction
6. 30-day cumulative incidence of ischemic stroke

Analysis Plan

See **Appendix F** for Output Tables.

1) Cohort selection (Table 1a, Table 1b, Table 1c): Apply inclusion and exclusion criteria to select the study cohorts. For Cohort B (GP), match to the kidney transplant recipients as described above. Provide the final cohort number by year.

2) Baseline characteristics (Table 2a, Table 2b, Table 2c): Provide frequencies and descriptive characteristics for baseline characteristics for the cohorts accrued in each era of the study period.
Report % missing data for each variable, as indicated.
Report categorical variables as proportions. Report continuous variables as means with standard deviations for data that is normally distributed or medians with interquartile ranges for skewed data.
Compare cohort characteristics, on an era basis, using the Chi-square test.

3) Primary outcome (Table 3a): For each era of the study period, report the number of recipients in that cohort era (i.e. got their kidney transplant that year), number of recipients from that cohort era who have evidence of either death or first major adverse cardiovascular event during the first 3 years of follow-up (myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, ischemic stroke), the 95% confidence limits for the incidence rate (Wilson score method), the total person-years of follow-up (censoring for the outcome, emigration, or end of follow-up), and the event rate per 100 person-years of follow-up. Repeat the analysis for matched Cohort B (GP).
For Cohort A (KTx) only:
i) Repeat the primary analysis using the exponential equation.
ii) Report the median [IQR] time to first event in years for each era.
iii) Breakdown of the type of event within 3 years of index date (death, myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, ischemic stroke). Sum of each type should equal the total number of events for each cohort era. Sum of the proportions for each cohort era should be 1.
iv) Stratify the primary analyses by age (<65 vs. ≥65), sex (female, male), and donor type (living donor, deceased donor). Report the number of events, the cumulative incidence, the 95% confidence limits, the total person-years of follow-up, and the event rate per 100 person-years of follow-up.
v) Calculate the incidence rate and 95% confidence limits for each era for the following time periods after transplantation using Poisson models: 0-3 months, 4-12 months, 13-36 months.

6) Secondary outcomes at 3 years (Table 3b):
Report the number of events, the cumulative incidence, the 95% confidence limits, the total person-years of follow-up, and the event rate per 100 person-years of follow-up for all 3 cohorts.

a) Death within 3 years of index date

b) First major adverse cardiovascular event within 3 years of index date

For Cohort A (KTx) only:
c) Major adverse cardiovascular event by type within 3 years of index date:
Here, the denominator is the total number of recipients in each cohort era
i) Myocardial infarction
ii) Percutaneous coronary intervention
iii) Coronary artery bypass graft surgery
iv) Ischemic stroke

d) Cardiac testing by type within 3 years of index date:
i) Carotid ultrasound
ii) Coronary angiogram
iii) Echocardiography
iv) Holter monitoring

v) Stress test

Compare the primary outcome, on an annual basis, using the Cochrane-Armitage test for linear trend. Use joinpoint regression to identify changes in linear slope.

7) Secondary outcomes at 30 days (Table 3c): To assess perioperative cardiovascular complications, report the total number of events, the cumulative incidence, and the 95% confidence limits for Cohort A (KTx) only:
i) Myocardial infarctions within 30 days of the index date
ii) Ischemic strokes within 30 days of the index date

Tables:

Appendices:

Appendix A: Exclusion Codes

Exclusion Variable	Databases	Codes
Non-Ontario resident	PRCDDABLK (using %getdemo)[a]	PR ≠ 35
Transplant - renal	CIHI-DAD: Source ☒ All Institution types ☒ Acute care (insttype = 'AP' or 'AT') Include suspected/questionable diagnoses? ☒ No OHIP: Claim Type ☒ NONLAB	 Renal Transplantation.xls  renal transplant.txt
Dialysis	CIHI-DAD: Source ☒ All Institution types ☒ Acute care (insttype = 'AP' or 'AT') Include suspected/questionable diagnoses? ☒ No OHIP: Claim Type ☒ NONLAB	 HD & PD dialysis and access exclusion 201  HD & PD dialysis and access exclusion 201
Chronic kidney disease	CIHI-DAD: Source ☒ All Institution types ☒ Acute care (insttype = 'AP' or 'AT') Include suspected/questionable diagnoses? ☒ No	 CKD final list.txt

[a] %getdemo is a combination of RPDB and PCCFyyyy datasets

Appendix B: Baseline Characteristics Codes

Baseline Characteristics	**Database(s)**	**Codes**
Age	RPDB	
Sex	RPDB	
Race	CORR Dataset: RECIPIENT - Variable: RACIAL_ORIGIN_CODE	
Income quintile	PSTLYEAR (using %getdemo)	
Rural location	PSTLYEAR (using %getdemo)	
Kidney-related Factors	**Database**	**Codes**
Date of transplant	CORR Dataset: RECIPIENT_TREATMENT - Variable: TREATMENT_CODE = 171 - Variable: TREATMENT_DATE - Variable: TRANSPLANTED_ORGAN_TYPE_CODE[1-3]	
Cause of end-stage renal disease	CORR Dataset: RECIPIENT_TREATMENT - Variable: PRIMARY_DIAGNOSIS_KIDNEY	See **Appendix C**
Donor type	CORR Dataset: TRANSPLANTED_KIDNEY - Variable: DONOR_TYPE_CODE	
Dialysis modality	CORR Dataset: RECIPIENT_TREATMENT - Variable: TREATMENT_CODE	See **Appendix D**
Dialysis vintage	CORR Dataset: RECIPIENT_TREATMENT - Variable: TREATMENT_DATE	
Dialysis	CIHI-DAD Source ☒ All Institution types ☒ Acute care (insttype = 'AP' or 'AT') Diagnosis Type (dxtype) ☒ All (alldx) Include suspected/questionable diagnoses? ☒ No OHIP Claim Type ☒ NONLAB	 HD & PD dialysis as an outcome 2014082  HD & PD dialysis as an outcome 2014082  HD Outcome 20140821.txt  PD Outcome 20140821.txt
Co-morbidities	**Database(s)**	**Codes**
Coronary artery disease without angina	CIHI-DAD Source ☒ All Institution types ☒ Acute care (insttype = 'AP' or 'AT') Diagnosis Type (dxtype)	 Coronary Artery Disease EX Angina 20

	☒ All (alldx) Include suspected/questionable diagnoses? ☒ No OHIP Claim Type ☒ NONLAB	 Coronary Artery Disease EX Angina 20
Myocardial infarction	CIHI-DAD Source ☒ All Institution types ☒ Acute care (insttype = 'AP' or 'AT') Diagnosis Type (dxtype) ☒ All (alldx) Include suspected/questionable diagnoses? ☒ No	 MI.x s  MI.txt
Percutaneous coronary intervention	CIHI-DAD Source ☒ All Institution types ☒ Acute care (insttype = 'AP' or 'AT') Include suspected/questionable diagnoses? ☒ No OHIP Claim Type ☒ NONLAB	 PCI 20141120.xlsx  PCI 20141120.txt
Coronary artery bypass graft surgery	CIHI-DAD Source ☒ All Institution types ☒ Acute care (insttype = 'AP' or 'AT') Include suspected/questionable diagnoses? ☒ No OHIP Claim Type ☒ NONLAB	 CABG 20141120.xls  CABG 20141120.txt
Heart failure	CIHI-DAD Source ☒ All Institution types ☒ Acute care (insttype = 'AP' or 'AT') Diagnosis Type (dxtype) ☒ All (alldx) Include suspected/questionable diagnoses? ☒ No OHIP Claim Type ☒ NONLAB	 CHF.xls  CHF.txt
Hypertension	CIHI-DAD Source ☒ All Institution types	 Hypertension 20140623.xls

	☒ Acute care (insttype = 'AP' or 'AT') Diagnosis Type (dxtype) ☒ All (alldx) Include suspected/questionable diagnoses? ☒ No OHIP Claim Type ☒ NONLAB Patients with hypertension are those that have evidence of two OHIP claims for hypertension OR one hospitalization with a diagnosis of hypertension within the three-year look-back window.	 Hypertension 20140623.txt
Diabetes	CIHI-DAD Source ☒ All Institution types ☒ Acute care (insttype = 'AP' or 'AT') Diagnosis Type (dxtype) ☒ All (alldx) Include suspected/questionable diagnoses? ☒ No OHIP Claim Type ☒ NONLAB Patient with diabetes are those that have evidence of two OHIP claims for diabetes OR one hospitalization with a diagnosis of diabetes within the three-year look-back window.	 diabetes mellitus baseline characteristi
Stroke/Transient ischemic attack (TIA)	CIHI-DAD Source ☒ All Institution types ☒ Acute care (insttype = 'AP' or 'AT') Diagnosis Type (dxtype) ☒ All (alldx) Include suspected/questionable diagnoses? ☒ No	 All Stroke (including TIA) 20141128.xls  All Stroke (including TIA) 20141128.txt
Cardiac Testing	**Database(s)**	**Codes**
Carotid ultrasound	CIHI-DAD: Source ☒ All Institution types ☒ Acute care (insttype = 'AP' or 'AT') Include suspected/questionable diagnoses? ☒ No OHIP: Claim Type ☒ NONLAB	 Carotid Ultrasound 20141120.xls  Carotid Ultrasound 20141120.txt

Coronary angiogram	CIHI-DAD: Source ☒ All Institution types ☒ Acute care (insttype = 'AP' or 'AT') Include suspected/questionable diagnoses? ☒ No OHIP: Claim Type ☒ NONLAB	
Echocardiography	CIHI-DAD: Source ☒ All Institution types ☒ Acute care (insttype = 'AP' or 'AT') Include suspected/questionable diagnoses? ☒ No OHIP: Claim Type ☒ NONLAB	
Holter monitoring	CIHI-DAD: Source ☒ All Institution types ☒ Acute care (insttype = 'AP' or 'AT') Include suspected/questionable diagnoses? ☒ No OHIP: Claim Type ☒ NONLAB	
Stress test	CIHI-DAD: Source ☒ All Institution types ☒ Acute care (insttype = 'AP' or 'AT') Include suspected/questionable diagnoses? ☒ No OHIP: Claim Type ☒ NONLAB	

Appendix C: CORR Codes for Primary Cause of End-Stage Renal Disease

Glomerulonephritis/Autoimmune Diseases	
05	Mesangial proliferative glomerulonephritis
06	Minimal lesion glomerulonephritis
07	Post-strep glomerulonephritis
08	Rapidly progressive glomerulonephritis
09	Focal glomerulosclerosis - adults
10	Glomerulonephritis, histologically NOT examined
11	Severe nephrotic syndrome with focal sclerosis (paed.)
12	IgA nephropathy - proven by immunofluorescence (not code 85)
13	Dense deposit disease - proven by immunofluorescence and/or electron microscopy (MPGN type II)
14	Membranous nephropathy
15	Membranoproliferative mesangiocapillary glomerulonephritis (MPGN type I)
16	Idiopathic crescentic glomerulonephritis (diffuse proliferative)
17	17 - Congenital Nephrosis/Cong.Nephrotic Syndrome (Paed.)
19	Glomerulonephritis, histologically examined - specify
73	Polyarteritis
74	Wegener's granulomatosis
84	Lupus erythematosus
85	Henoch-Schõnlein purpura
86	Goodpasture syndrome
88	Hemolytic uremic syndrome (Moschcowitz syndrome)
Cystic Kidney Disease	
40	Cystic kidney disease, type unspecified
41	Polycystic kidneys, adult type (dominant)
42	Polycystic kidneys, infantile and juvenile types (recessive)
43	Medullary cystic disease, including nephronophthisis
49	Cystic kidney disease, other type - specify
Diabetes	
80	Diabetic nephropathy associated with type 1
81	Diabetic nephropathy associated with type 2
Renal Vascular Disease	
70	Renal vascular disease, type unspecified
71	Malignant hypertension (no primary renal disease)
72	Renal vascular disease due to hypertension (no primary renal disease)
79	Renal vascular disease, classified (nephrosclerosis, renal vascular thrombosis)
Other	
20	Pyelonephritis/interstitial nephritis, cause not specified
21	Pyelonephritis/interstitial nephritis associated with neurogenic bladder
22	Pyelonephritis/interstitial nephritis due to congenital obstructive uropathy with or without vesicoureteric reflux

23	Pyelonephritis/interstitial nephritis due to acquired obstructive uropathy - specify
24	Pyelonephritis/interstitial nephritis due to vesicoureteric reflux without obstruction
25	Pyelonephritis/interstitial nephritis due to urolithiasis
29	Pyelonephritis, other causes
30	Nephropathy caused by drugs or nephrotoxic agents, cause not specified
31	Nephropathy due to analgesic drugs
32	Nephropathy due to cisplatin
33	Nephropathy due to Cyclosporin A
39	Nephropathy caused by other specific drug - specify
50	Hereditary familial nephropathy, type unspecified
51	Hereditary nephritis with nerve deafness (Alport syndrome)
52	Cystinosis
53	Oxalosis
54	Fabry disease
55	DRASH syndrome
56	Sickle cell nephropathy
57	Wilms' tumour
58	Posterior urethral valves
59	Hereditary nephropathy, other - specify
60	Congenital renal hypoplasia - specify
61	Oligomeganephronic hypoplasia
62	Segmental renal hypoplasia (Ask-Upmark kidney)
63	Congenital renal dysplasia with or without urinary tract malformation
66	Syndrome of agenesis of abdominal muscles (prune belly syndrome)
78	Atheroembolic renal disease
82	Multiple myeloma
83	Amyloid
87	Scleroderma
89	Multi-system disease, other - specify
90	Cortical or acute tubular necrosis
91	Tuberculosis
92	Gout
93	Nephrocalcinosis and hypercalcemic nephropathy
94	Balkan nephropathy
95	Kidney tumour
96	Traumatic or surgical loss of kidney
97	HIV nephropathy
99	Other identified renal disorders - specify
Unknown	
00	Chronic renal failure - etiology uncertain
98	Unknown

Appendix D: CORR Codes for Treatment Codes for Dialysis

Hemodialysis	
111	1 - Acute Care Hospital, 1 - Conventional Haemodialysis, 1 - Total Care
112	1 - Acute Care Hospital, 1 - Conventional Haemodialysis, 2 - Limited Self Care
113	1 - Acute Care Hospital, 1 - Conventional Haemodialysis, 3 - Total Self Care
121	1 - Acute Care Hospital, 2 - Short Daily Haemodialysis, 1 - Total Care
122	1 - Acute Care Hospital, 2 - Short Daily Haemodialysis, 2 - Limited Self Care
123	1 - Acute Care Hospital, 2 - Short Daily Haemodialysis, 3 - Total Self Care
131	1 - Acute Care Hospital, 3 - Slow Nocturnal Haemodialysis, 1 - Total Care
132	1 - Acute Care Hospital, 3 - Slow Nocturnal Haemodialysis, 2 - Limited Self Care
133	1 - Acute Care Hospital, 3 - Slow Nocturnal Haemodialysis, 3 - Total Self Care
211	2 - Chronic Care Hospital, 1 - Conventional Haemodialysis, 1 - Total Care
221	2 - Chronic Care Hospital, 2 - Short Daily Haemodialysis, 1 - Total Care
231	2 - Chronic Care Hospital, 3 - Slow Nocturnal Haemodialysis, 1 - Total Care
311	3 - Community Centre, 1 - Conventional Haemodialysis, 1 - Total Care
312	3 - Community Centre, 1 - Conventional Haemodialysis, 2 - Limited Self Care
313	3 - Community Centre, 1 - Conventional Haemodialysis, 3 - Total Self Care
321	3 - Community Centre, 2 - Short Daily Haemodialysis, 1 - Total Care
322	3 - Community Centre, 2 - Short Daily Haemodialysis, 2 - Limited Self Care
323	3 - Community Centre, 2 - Short Daily Haemodialysis, 3 - Total Self Care
331	3 - Community Centre, 3 - Slow Nocturnal Haemodialysis, 1 - Total Care
332	3 - Community Centre, 3 - Slow Nocturnal Haemodialysis, 2 - Limited Self Care
333	3 - Community Centre, 3 - Slow Nocturnal Haemodialysis, 3 - Total Self Care
413	4 - Home, 1 - Conventional Haemodialysis, 3 - Total Self Care
423	4 - Home, 2 - Short Daily Haemodialysis, 3 - Total Self Care
433	4 - Home, 3 - Slow Nocturnal Haemodialysis, 3 - Total Self Care
Peritoneal Dialysis	
141	1 - Acute Care Hospital, 4 - CAPD, 1 - Total Care
151	1 - Acute Care Hospital, 5 - APD, 1 - Total Care
152	1 - Acute Care Hospital, 5 - APD, 2 - Limited Self Care
241	2 - Chronic Care Hospital, 4 - CAPD, 1 - Total Care
242	2 - Chronic Care Hospital, 4 - CAPD, 2 - Limited Self Care
251	2 - Chronic Care Hospital, 5 - APD, 1 - Total Care
252	2 - Chronic Care Hospital, 5 - APD, 2 - Limited Self Care
443	4 - Home, 4 - CAPD, 3 - Total Self Care
453	4 - Home, 5 - APD, 3 - Total Self Care
Other	
060	0 - Treatment-dependent Locations, 6 - PD combined with HD, 0 - Other

Appendix E: Diagnostic Codes for Outcome Variables

CIHI-DAD

Diagnosis Type (dxtype)
☒ Most responsible diagnosis (M)
(except where indicated e.g. alldx for 30-day outcome of acute MI and ischemic stroke)

Outcome Variable	Database(s)	Codes
Death	RPDB	Vital status field
Myocardial infarction	CIHI–diagnostic	  MI.txt
Ischemic stroke	CIHI-diagnostic	 Ischemic Stroke 20140623.xls  Ischemic Stroke 20140623.txt
Percutaneous coronary intervention	CIHI-procedure OHIP-procedure	 PCI 20141120.xlsx  PCI 20141120.txt
Coronary artery bypass graft surgery	CIHI-procedure OHIP-procedure	 CABG 20141120.xls  CABG 20141120.txt
Cardiac testing	CIHI-procedure OHIP-procedure	See **Appendix B**

Appendix F: Outcome Tables

Appendix 2: STROBE checklist.(34)

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

		and interactions	
		(c) Explain how missing data were addressed	Methods
		(d) If applicable, explain how loss to follow-up was addressed	Not applicable
		(e) Describe any sensitivity analyses	Not applicable
Results			
Participants	13	(a) Report numbers of individuals at each stage of study—e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed	Results Figure 1
		(b) Give reasons for non-participation at each stage	Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders	Results Table 2 Table 3
		(b) Indicate number of participants with missing data for each variable of interest	Table 2
		(c) Summarize follow-up time (e.g. average and total amount)	Results
Outcome data	15	Report numbers of outcome events or summary measures over time	Results Table 4 Table 6
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g. 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Results Table 4 Table 6
		(b) Report category boundaries when continuous variables were categorized	Table 1
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses	Results
Discussion			
Key results	18	Summarize key results with reference to study objectives	Discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Discussion
Interpretation	20	Give a cautious overall interpretation of results	Discussion

		considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	
Generalizability	21	Discuss the generalizability (external validity) of the study results	Discussion
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Disclosure

Appendix 3: Databases and coding definitions.

Variable	Database	Codes
Inclusion/Exclusion Criteria		
Kidney transplantation	CIHI-diagnostic	ICD-9: V42.0, 996.81
	CIHI-diagnostic	ICD-10: N16.5, T86.1, Z94.0
	CIHI-procedure	CCP: 67.43, 67.5
	CIHI-procedure	CCI: 1PC85
	OHIP-procedure[a]	OHIP: E762, E769, E771, G347, G348, G408, G409, G412, S434, S435, Z631
	CORR	Treatment_code: 171, 181 Transplanted_organ_type_code [1-3]: 10, 11, 12, 18, 19
Dialysis	CIHI-diagnostic	ICD-9: V45.1, V56.0, V56.8, 996.73
	CIHI-diagnostic	ICD-10: T82.4, Y60.2, Y61.2, Y62.2, Y84.1, Z49, Z99.2
	CIHI-procedure	CCP: 51.27, 51.42, 51.43, 51.95, 66.98
	CIHI-procedure	CCI: 1JM76NC, 1JM76NCXXN, 1KG76MZXXA, 1KG76MZXXN, 1KY76, 1PZ21, 1OT53DATS, 1OT53HATS, 1OT53LATS, 1SY55LAFT, 7SC59QD
	OHIP-procedure[a]	OHIP: G082, G083, G085, G090, G091, G092, G093, G094, G095, G096, G099, G294, G295, G323, G324, G325, G326, G327, G330, G331, G332, G333, G336, G860, G861, G862, G863, G864, G865, G866, H540, H740, R825, R826, R827, R833, R840, R841, R843, R848, R849, R850, R851, R852, R853, R854, R885, R941, R942, R943, R944, R945, R946, Z450, Z451, Z452
Chronic kidney disease	CIHI-diagnostic	ICD-9: 250.4, 403.0, 403.1, 403.9, 404.0, 404.1, 404.9, 585, 586, 588.8, 588.9
	CIHI-diagnostic	ICD-10: E10.2, E11.2, E13.2, E14.2, I12, I13, N08, N18, N19
	OHIP-diagnostic	OHIP: 403, 585

Baseline Characteristics - Demographics		
Age, Sex, Socioeconomic status, Rural location	RPDB	
Race	CORR	Racial_origin_code: Caucasian: 01 Asian: 02 African-American: 03 Indian: 05 Other: 08, 09, 10, 11, 99 Unknown: 98
Baseline Characteristics – Kidney-Related Characteristics		
Transplant date	CORR	
Cause of ESRD	CORR	Primary_diagnosis_kidney: Glomerulonephritis/Auto-immune disease: 05, 06, 07, 08, 09, 10, 11, 12, 13, 14, 15, 16, 17, 19, 73, 74, 84, 85, 86, 88 Diabetes: 80, 81 Cystic kidney disease: 40, 41, 42, 43, 49 Renal vascular disease: 70, 71, 72, 79 Other: 20, 21, 22, 23, 24, 25, 29, 30, 31, 32, 33, 39, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 66, 78, 82, 83, 87, 89, 90, 91, 92, 93, 94, 95, 96, 97, 99 Unknown: 00, 98
Donor type	CORR	Donor_type_code: Living: 02, 03, 04, 05, 06, 07, 10, 12, 15 Deceased: 01 Unknown/Out-of-country transplant: 98
Dialysis modality	CORR	Treatment_code: Hemodialysis: 111, 112, 113, 121, 122, 123, 131, 132, 133, 211, 221, 231, 311, 312, 313, 321, 322, 323, 331, 332, 333, 413, 423, 433 Peritoneal dialysis: 141, 151, 152, 241, 242, 251, 252, 443, 453 Other: 060
Dialysis vintage	CORR	Treatment_date
Dialysis	CIHI-procedure CIHI-procedure	CCP: 51.95, 66.98 CCI: 1PZ21

	OHIP-procedure[a]	OHIP: G082, G083, G085, G090, G091, G092, G093, G094, G095, G096, G294, G295, G323, G325, G326, G330, G331, G332, G333, G860, G861, G862, G863, G864, G865, G866, H540, H740, R849
Baseline Characteristics – Co-morbidities		
Coronary artery disease	CIHI-diagnostic	ICD-9: 410, 411, 412
	CIHI-diagnostic	ICD-10: I21, I22, T82.2, Z95.5
	CIHI-procedure	CCP: 48.01, 48.02, 48.03, 48.04, 48.05, 48.1, 48.2, 48.3
	CIHI-procedure	CCI: 1IJ50, 1IJ76
	OHIP-diagnostic	OHIP: 410, 412
	OHIP-procedure[a]	OHIP: E646, E651, E652, E654, E655, G298, R741, R742, R743, Z434, Z448
Hypertension[b]	CIHI-diagnostic	ICD-9: 401, 402, 403, 404, 405
	CIHI-diagnostic	ICD-10: I10, I11, I12, I13, I15
	OHIP-diagnostic	OHIP: 401, 402, 403
Diabetes[b]	CIHI-diagnostic	ICD-9: 250
	CIHI-diagnostic	ICD-10: E10, E11, E13, E14
	OHIP-diagnostic	OHIP: 250
	OHIP-procedure[a]	OHIP: K029, K030, Q040
Myocardial infarction	CIHI-diagnostic	ICD-9: 410
	CIHI-diagnostic	ICD-10: I21, I22
PCI	CIHI-procedure	CCP: 48.02, 48.03, 48.09
	CIHI-procedure	CCI: 1IJ50, 1IJ54GQAZ, 1IJ57GQ
	OHIP-procedure[a]	OHIP: G262, G298, Z434
CABG surgery	CIHI-procedure	CCP: 48.11, 48.12, 48.13, 48.14, 48.15, 48.16, 48.17, 48.19
	CIHI-procedure	CCI: 1IJ76

	OHIP-procedure	OHIP: E645, E646, E652, E654, R742, R743
Heart failure	CIHI-diagnostic	ICD-9: 425, 428, 514, 518.4
	CIHI-diagnostic	ICD-10: I25.5, I50.0, I50.1, I50.9, J81
	CIHI-procedure	CCP: 49.61, 49.62, 49.63, 49.64
	CIHI-procedure	CCI: 1HP53, 1HP55, 1HZ53GRFR, 1HZ53LAFR, 1HZ53SYFR
	OHIP-diagnostic	OHIP: 428
	OHIP-procedure[a]	OHIP: R701, R702, Z429
Stroke/TIA	CIHI-diagnostic	ICD-9: 362.3, 430, 431, 432, 434, 435, 436
	CIHI-diagnostic	ICD-10: G45.0, G45.1, G45.2, G45.3, G45.8, G45.9, H34.0, H34.1, I60.0, I60.1, I60.2, I60.3, I60.4, I60.5, I60.6, I60.7, I60.9, I61, I62, I63.0, I63.1, I63.2, I63.3, I63.4, I63.5, I63.8, I63.9, I64
Baseline Characteristics – Cardiovascular Investigations		
Holter monitor	CIHI-procedure	CCP: 03.54
	CIHI-procedure	CCI: 2HZ24JAKH
	OHIP-procedure[a]	OHIP: G311, G320, G647, G648, G649, G650, G651, G652, G653, G654, G655, G656, G657, G658, G659, G660, G661, G682, G683, G684, G685, G686, G687, G688, G689, G690, G692, G693
Echocardiography	CIHI-procedure	CCP: 02.82
	CIHI-procedure	CCI: 3IP30
	OHIP-procedure[a]	OHIP: G560, G561, G562, G566, G567, G568, G570, G571, G572, G574, G575, G576, G577, G578, G581
Stress test	CIHI-procedure	CCP: 03.41, 03.42, 03.43, 03.44, 06.05
	CIHI-procedure	CCI: 2HZ08, 3IP70
	OHIP-procedure[a]	OHIP: G111, G112, G174, G315, G319, G582, G583, G584,

		J607, J608, J609, J666, J807, J808, J809, J866	
Coronary angiogram	CIHI-procedure CIHI-procedure OHIP-procedure[a]	CCP: 48.92, 48.93, 48.94, 48.95, 48.96, 48.97, 48.98 CCI: 3IP10, 3IS10 OHIP: G297, G509	
Carotid ultrasound	CIHI-procedure CIHI-procedure OHIP-procedure[a]	CCP: 02.81 CCI: 3JE30, 3JG30 OHIP: J190, J191, J201, J490, J491, J492, J501	
Outcome Measurements			**Validity**[c,d]
Death (68)	RPDB	Vital status field	Sensitivity: 94% PPV: 100%
Myocardial infarction (69,70)	CIHI-diagnostic	As above	For ICD-9 codes: Sensitivity: 89% PPV: 90% For ICD-10 codes:[e] Sensitivity: 89% PPV: 87%
PCI (71)	CIHI-procedure OHIP-procedure[a]	As above	For CCI codes: PPV: 94-96%
CABG (71)	CIHI-procedure OHIP-procedure[a]	As above	For CCI codes: PPV: 97-98%
Ischemic stroke (72)	CIHI-diagnostic CIHI-diagnostic	ICD-9: 434, 436 ICD-10: H34.1, I63.0, I63.1, I63.2, I63.3, I63.4, I63.5, I63.8, I63.9, I64	For ICD-9 codes: PPV: 86-92%
Cardiovascular investigation	CIHI-procedure OHIP-procedure[a]	As above	

[a] Approximately 95% of Ontario physicians operate under the fee for service payment structure of the Ontario Health Insurance Plan (OHIP). The sensitivity and positive predictive value of these procedure codes is expected to be high, as shown with other service payments.(73) Other studies have reported the value of using physician billing data in combination with other administrative healthcare data to improve the identification of relevant procedures.(74)

[b] Defined as evidence of 2 OHIP claims *or* 1 hospitalization with a diagnostic claim within the 3-year look-back window.
[c] Information regarding specificity and negative predictive value is omitted. In almost all instances these parameters were high and precise because of the low underlying prevalence of the diagnoses or procedures in the dataset.
[d] Validation performed against the following reference standards: chart review,(68) patient registry,(69) chart abstraction and recoding.(70–72) Diagnostic conditions were considered present in the discharge abstract for any hospitalization if it was listed as the primary reason for the majority of length of hospital stay.
[e] Added ICD-10 code I22 (subsequent myocardial infarction).
Abbreviations: CABG, coronary artery bypass graft; CCI, Canadian Classification of Health Interventions; CCP, Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures; CIHI, Canadian Institute for Health Information; CORR, Canadian Organ Replacement Register; ESRD, end-stage renal disease; ICD-9; International Classification of Diseases, 9th Revision; ICD-10, International Classification of Diseases, 10th Revision; OHIP, Ontario Health Insurance Plan; PCI, percutaneous coronary intervention; PPV, positive predictive value; RPDB, Registered Persons Database; TIA, transient ischemic attack.

Curriculum Vitae

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Bachelor of Science (Honours), Life Sciences
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Post-graduate Training:

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Clinical Investigator Program
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Faculty Scholars Program
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Summer Research Scholarship
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Chernoff Family Entrance Scholarship
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Chief Medical Resident
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Publications:

1. Li AH, **Lam NN**, Naylor KL, Garg AX, Knoll GA, Kim SJ. Early hospital readmissions after transplantation: Causes, consequences, and costs. *Transplantation* 2015 [Submitted]

2. Naylor KL, Jamal SA, Zou G, Leslie WD, McArthur E, **Lam NN**, Knoll GA, Kim SJ, Fraser L, Adachi JD, Holdsman AB, Garg AX. Frequency of bone mineral density testing in adult kidney transplant recipients. *American Journal of Transplantation* 2015 [Submitted]

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