Epidemiology of Ischemic Heart Disease in Patients with Chronic Kidney Disease in Alberta

by

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Abstract

Background: Cardiovascular disease (CVD) is a leading cause of morbidity and mortality in patients with chronic kidney disease (CKD). Patients with CKD and CVD are often excluded from randomized control trials leading to a paucity of evidence guiding their care. This study leveraged province-wide administrative health data in Alberta to describe the epidemiology of ischemic heart disease (IHD). We examined the temporal trends in the burden of IHD and acute myocardial infarction (AMI) and processes of care in patients with CKD in Alberta.

Methods and Results: Using the Alberta Kidney Disease Network database, we created a cohort of patients (aged 18 years and above) who received a diagnosis of IHD between 2003 and 2019. The number of IHD cases, non-ST elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI) episodes were determined by standard definitions and frameworks (international classification of diseases (ICD) codes, procedural and physician billing codes). Processes of care was determined by identifying the proportion of patients that received guideline-recommended medications and/or procedures (coronary artery revascularization), and achievement of quality of care markers of (LDL, HbA1c and albuminuria) within the 12 months following a diagnosis of IHD and 6 months following a diagnosis of STEMI or NSTEMI. Individuals were categorized based on level of kidney function by KDIGO criteria (stage G1/G2 eGFR >60 ml/min/1.73m^2, stage G3 eGFR 59 – 30 ml/min/1.73m^2, stage G4 eGFR 29 – 15 ml/min/1.73m^{22} and stage G5 eGFR <15 ml/min/1.73m^2.

Results: A total of 522,961 individuals were diagnosed with IHD in Alberta between 2003 and 2019 and were included in our study cohort. These individuals were categorized based on their level of kidney function according to KDIGO criteria. Between 2003 and 2019, there was an increase in the age and sex-standardized prevalence of IHD across all levels of kidney function and a decrease in the annual incidence of STEMI and NSTEMI for most stages of CKD. Within the 12 months following a diagnosis of IHD, patients with an eGFR ≥ 60 ml/min/1.73m² filled relatively fewer prescriptions for ACEi/ARB, statins, and beta blockers than patients with an eGFR < 60 ml/min/1.73m². Within the 6 months following the diagnosis of STEMI and NSTEMI, as eGFR declined, fewer patients received guideline-recommended medications and, in general, fewer patients achieved LDL < 2 mmol/L and urinary ACR < 3 mg/mmol. Additionally, in the 6 months following the diagnosis of STEMI and NSTEMI, fewer patients underwent invasive coronary revascularization as eGFR declined.

Conclusion: Between 2003 and 2019, the prevalence of IHD increased across all stages of CKD, and there was a concomitant decreasing trend in the incidence of acute forms of IHD (STEMI and NSTEMI). This may reflect the increasing longevity of patients with IHD and CKD in Alberta during this period because of improvements in their care. Guideline-based medications were utilized more frequently in patients with CKD and IHD and less frequently in patients with CKD and STEMI or NSTEMI. PCI and CABG performed less frequently in patients with CKD, with their use inversely associated with eGFR. Future studies should better clarify the factors that mediate the

association between eGFR and treatment for IHD, STEMI, and NSTEMI, as well as look at clinically important outcomes in patients with CKD.

Preface

The research conducted for this thesis forms part of a research collaboration, led by Professors Aminu K Bello, Gavin Oudit and the Alberta Kidney Disease Network (AKDN) at the University of Alberta. The work covering my thesis (development of study protocol, analysis plan and report) is conducted by myself, with the assistance of my supervisory committee. The data analysis was conducted jointly with an analysist with the AKDN. The research project that forms the basis of this thesis received research ethics approval from the University of Alberta Research Ethics Board, Pro00122861.

Parts of this thesis have been presented at the following conferences:

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Dedication

I dedicate this thesis to my friends, family, and my partner, Samra. Your support and encouragement have helped me throughout this journey. Thank you for believing in me.

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The data analysis was performed with the support of Feng Ye, statistician at the University of Alberta, Faculty of Medicine and Dentistry, Department of Medicine.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

ACEi	Angiotensin-converting enzyme inhibitor
ACR	Albumin-creatinine ratio
ACS	Acute coronary syndrome
AMI	Acute myocardial infarction
ARB	Angiotensin receptor blocker
CAD	Coronary artery disease
CKD	Chronic kidney disease
CVD	Cardiovascular disease
eGFR	Estimated glomerular filtration rate
FFS	Fee-for-service
ICD	International classification of diseases
IHD	Ischemic heart disease
NSTEMI	Non-ST-elevation myocardial infarction
PCI	Percutaneous coronary intervention
PCR	Protein-creatinine ratio
PPCI	Primary percutaneous coronary intervention
SGLT2i	Sodium-glucose co-transporter-2 inhibitor
STEMI	ST-elevation myocardial infarction

Chapter 1.

Introduction

1.1 Background

Cardiovascular disease (CVD) is a leading cause of morbidity and mortality in patients with chronic kidney disease (CKD) (1). The risk for CVD-related mortality is higher in patients with kidney failure treated with dialysis or transplant as well as in non-dialytic CKD patients compared to the general population (2). For example, the mortality rate after myocardial infarction is several-fold higher in CKD and dialysis patients (3,4). Patients with CKD appear to be predisposed to CVD not only from traditional CVD risk factors, including type 2 diabetes, hypertension, and dyslipidemia, but also due to non-traditional factors that are related to the uremic milieu, including vascular endothelial dysfunction and inflammation (1). The mechanistic pathways are linked to retention of uremic toxins, abnormalities in bone metabolism, anemia, vascular remodeling and dialysis related factors (1,5). Despite the high prevalence of CVD among patients with CKD, patients with CKD are frequently excluded from randomized control trials of cardiovascular interventions (6,7). It has been suggested that this may be due to concern for adverse effects from medications in patients with CKD, nephrotoxicity associated with contrast dye and the possibility that including patients with CKD in trials may lead to null results as the pathophysiologic mechanisms of their cardiovascular disease differs from the general population (6–8). The net result is underrepresentation of patients with CKD in cardiovascular disease trials and has led to a paucity of evidence informing the care of patients with CKD and CVD. Thus, despite the high burden of CVD in patients with chronic kidney disease, they often receive suboptimal medical care and interventions such as coronary angiography are frequently underused in this patient population (8,9).

1.1. Trend in cardiovascular disease in patients with chronic kidney disease

It is well established that impaired kidney function is an independent risk factor for a variety of cardiovascular diseases (10). For example, analysis of the Atherosclerosis Risk in Communities (ARIC) prospective cohort, which followed 14, 857 middle aged American adults

from 1987 through 2002, found that the adjusted relative hazard ratio of developing heart failure was 1.94 (1.49 to 2.53) for individuals with eGFR 60 mL/min per 1.73 m² compared to the reference group with eGFR ≥ 90 (11). Separate analysis of the ARIC cohort similarly found that CKD independently increases the risk for other cardiovascular diseases, including stroke, peripheral artery disease, coronary heart disease and atrial fibrillation (12–15).

CKD does not only lead to cardiovascular disease, but studies have also shown that the risk of cardiovascular disease mortality is significantly greater in patients with CKD compared to the general population. For example, in one meta-analysis of 10 cohorts with 266, 975 patients found that the association between eGFR and the relative risk for all-cause mortality and cardiovascular mortality steadily increased at eGFRs below 60 ml/min per 1.73 m² (16). This study found that for cardiovascular mortality, the adjusted hazard ratios were 1.11 (0.93–1.32), 1.73 (1.49–2.00), and 3.08 (1.89–5.01) for eGFRs 60, 45, and 15 ml/min per 1.73 m², respectively (16). The adjusted hazard ratios for cardiovascular disease mortality were 1.11 (0.93–1.32), 1.73 (1.49–2.00), and 3.08 (1.89–5.01) for eGFRs 60, 45, and 15 ml/min per 1.73 m2, respectively (16). Similarly, in a Canadian cohort of 949, 119 people, when adjusted for age and sex, cardiovascular disease accounted for 27.5% of deaths in individuals with normal kidney function versus 58.0% in those with kidney failure (17,18).

There is some evidence that globally, patients with CKD and CVD, may be experiencing improved clinical outcomes over time (3,19–24). In the US Renal Data System database 2023 Annual Report, the adjusted rates of hospitalization for cardiovascular disease in patients with CKD who were Medicare fee-for-service (FFS) beneficiaries aged ≥ 66 years decreased dramatically in 2020, after being stable between 2013-2019 and slightly increasing in 2022 (20). Studies have also shown that, in the United States, uptake of evidence-based cardiac therapies have increased between 2006 and 2012 in patients with AMI and CKD, and that PCI is associated with a lower risk of hospital mortality across all stages of CKD following both STEMI and NSTEMI (24). An analysis of the Japanese Society of Dialysis Therapy registry found that all-cause mortality in dialysis patients significantly decreased from 1988 to 2013 and that this was mainly due to decreased deaths from cardiovascular disease (19).

1.2. Definition: ischemic heart disease

Although it is well established that patients with CKD suffers a disproportion burden of all forms of CVD, the focus of this thesis will be ischemic heart disease (IHD) which is a term generally used to describe the pathophysiological state of an inadequate supply of blood to the myocardium due to obstruction of the coronary arteries that is commonly the result of atherosclerosis (25). IHD will be used as an umbrella term that encompasses both acute and stable coronary syndromes (25). Acute coronary syndromes (ACS) result from sudden reduction in coronary blood flow causing myocardial ischemia and variable degrees of damage to the myocardium called myocardial infarction (25). ACS can be sub-classified as either ST-elevation myocardial infarctions (STEMI), non-ST elevation myocardial infarctions (NSTEMI) or unstable angina based on the clinical context, associated ECG changes and presence or absence of biomarkers of myocardial damage when a patient presents in an appropriate clinical context (26–28).

Acute coronary syndromes are in contrast to stable coronary artery disease which results from reductions in coronary blood flow (25). Stable coronary artery disease includes patients who have received treatment for an ACS and have been discharged in stable condition as well as patients with ischemic cardiomyopathy, stable angina and those diagnosed with coronary artery disease based on the results of screening tests (29). I will elaborate next on the management of IHD based on the current state of the evidence, and specific elements to consider in patients with CKD.

1.3. Management of ischemic heart disease

This comprises of acute management for patients presenting with acute coronary syndromes as well as long-term medical management for patients with stable ischemic heart disease (26,27). For patients presenting with STEMI, immediate reperfusion, either with fibrinolysis or, preferably, coronary angiography and percutaneous coronary intervention (PCI) as needed is recommended (26). Among patients with NSTEMI, an immediate invasive strategy with angiography and PCI if indicated is recommended for patients presenting with very high-risk criteria, for example hemodynamic instability, and an inpatient invasive strategy, within the first 24 hours, is suggested for patients with high-risk criteria (26). Guidelines recommend that

PCI should be performed in patients with ACS and moderate-severe CKD (stage 2-3), citing that there is no current evidence of benefit in those with severe CKD or those who are dialysis dependent. In addition to immediate coronary artery reperfusion in patients presenting with STEMI and an early invasive strategy in high risk patients presenting with NSTEMI all patients with a new diagnosis of ACS are started on anti-platelet therapy with daily low dose aspirin in combination with a P2Y12 inhibitor for a limited duration unless there is an indication for anti-coagulation (26).

After management of the initial acute coronary syndrome event, the long-term medical management follows the same guidelines for patients with stable ischemic heart disease, which includes high intensity-statin therapy, anti-platelet therapy, disease modifying therapies and anti-anginal medications in addition to risk factor modification as tolerated, irrespective of their degree of kidney (26,29). High intensity statin therapy should be initiated regardless of initial LDL-values with the recommended reduction differing based on the guidelines and year of publication (26,29). The Canadian Cardiovascular Society (2016) recommended that patients with atherosclerotic cardiovascular disease obtain a target LDL-C <2.0 mmol/L or >50% reduction from baseline (30). For patients with CKD, the KDIGO guidelines recommend against a treat to target approach for patients with CKD in favour of a "fire and forget" approach (31). Disease modifying therapies include, beta blockers for patients with a left ventricular ejection fraction of $\leq$ 40%, ACE inhibitors (ACEi) for patients with heart failure symptoms, LVEF $\leq$ 40%, diabetes, hypertension and/or CKD and SGLT2 inhibitors for patients with heart failure or type 2 diabetes (26,29). Risk factor modification includes life-style modification as well as medical management of hypertension, preferably with ACE inhibitors, ARBs or beta blockers as well as glycemic control targeting HbA1c of ~7.0% for most adults with diabetes (29,32).

1.4. Coronary artery revascularization in patients with ischemic heart disease and chronic kidney disease

Studies evaluating clinical outcomes of coronary artery revascularization in patients with CKD and IHD compared to medical therapy alone have largely produced positive results. Three systematic reviews evaluating the treatment of ischemic heart disease (IHD) and acute coronary syndromes (ACS) in patients with CKD suggested that there is benefit from invasive coronary

artery revascularization. A 2009 systematic review and meta-analysis of five randomized control trials that enrolled 1,453 patients with CKD who were admitted to hospital with unstable angina or NSTEMI found that an early invasive strategy reduced the risk for rehospitalization and was associated with a trend towards reduction in the risk for death (33). A 2013 meta-analysis of 7 observational studies that included 23,234 patients found that early revascularization following ACS was associated with a reduction in 1 year mortality compared to medical therapy alone among patients with eGFR <60 ml/min/1.73m2 OR of 0.46 (95% CI: 0.26-0.82; p=0.008) and that the reduction in mortality persisted at 3 years across all CKD stages (34). A 2016 systematic review and meta-analysis of 10 studies with data from 147,908 patients found that an early invasive approach after NSTEMI conferred a survival benefit in patients with early to moderate CKD with a relative risk (RR) of 0.76 (95% CI: 0.49, 1.17) in randomized control studies and RR of 0.50 (95% CI: 0.42, 0.59) in observational studies (35).

One recent large prospective cohort study also provided evidence that favored invasive coronary artery revascularization over conservative treatment in CKD patients with stable ischemic heart disease (SIHD). The APPROACH prospective cohort study compared patients with CKD and SIHD in Alberta who underwent coronary angiography between January 1st 1999 and March 31st 2014 to patients who received medical therapy (36). This study showed that patients with CKD had significantly lower odds of receiving coronary revascularization compared to patients without CKD and that revascularization was associated with improved long-term survival across all stages of CKD including patients that were dialysis dependent (36).

The results of these studies are in contrast to the findings of the ISCHEMIA-CKD trial (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches-Chronic Kidney Disease), the first randomized control trial to look at differences in clinical outcomes for patients with advanced CKD and coronary artery disease (CAD) treated with either revascularization or medical management (37). This study randomly assigned 777 patients with advanced kidney disease and moderate or severe ischemia to either coronary angiography and revascularization, if indicated, with medical therapy or medical therapy alone. After a median follow-up of 2.2 years, the study found that that there was no difference in the primary composite outcome of death or nonfatal myocardial infarction between patients in the invasive-strategy group compared to the conservative-strategy group (37).

1.5. Research question

There is evidence of a global trend towards improved care and better clinical outcomes for patients with CKD and IHD, however it is unclear whether patients in a Canadian context have been experiencing similar improvements in care and outcomes over time. The research question of this thesis is two-fold: to determine the epidemiology of IHD in a Canadian CKD patient population and to identify differences in the processes of care received by patients with CKD and IHD compared to the general population with normal kidney function. The first question was addressed by studying trends in prevalence of IHD as well as prevalence and incidence of STEMI and NSTEMI in patients with CKD in Alberta. The second question was addressed by comparing the proportion of patients with CKD and IHD that received guideline recommended medications and/or procedures such as, percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) as well as attainment of treat targets for dyslipidemia (serum LDL levels), glycemic control (Hba1c) and proteinuria (urinary albumin: creatinine ratio).

1.6. Aims and hypothesis

The first aim was to describe the burden (prevalence and incidence) of IHD and AMI in patients with CKD across various stages in Alberta. The second aim of this thesis was to determine if there are differences in the processes of care received by patients with CKD and IHD compared to the general population with a normal kidney function. We hypothesized that the burden of IHD and AMI will be greater, and processes of care received will be lower compared to the general population without CKD in Alberta.

Chapter 2.

Methodology

2.1. Study population and data sources

The study cohort was comprised of patients over the age of 18 living in Alberta, Canada, who were diagnosed with ischemic heart disease, and had at one least outpatient serum creatinine measurement between May 1st, 2002 and March 31, 2019. We obtained data from the Alberta Kidney Disease Network (AKDN) database, which incorporates data from Alberta Health such as provincial health registry status, physician claims, hospital discharge abstracts, and ambulatory care utilization; the Northern and Southern Alberta Renal Programs to capture patients receiving chronic dialysis; and clinical laboratories in Alberta (17). We obtained drug prescription information from the Pharmaceutical Information Network (PIN) database. We excluded participants who had progressed to kidney failure and had received chronic dialysis or a kidney transplant. The study was approved by health research ethics boards at the Universities of Alberta and Calgary.

2.2. Identification of chronic kidney disease

We used the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation to calculate the estimated glomerular filtration rate (eGFR) (38). CKD was defined as at least two outpatient serum creatinine measurements greater than ninety days apart with eGFR values of less than 60 ml/min/1.73m^2 (4). The date of the second qualifying serum creatinine measurement was used as the index date for each patient. Baseline eGFR was defined as the index eGFR, and it was categorized as 45-60, 30-44, 15-29, or <15 ml/min/1.73 m^2 based on the 2012 KDIGO stages of CKD (4). Individuals who did not meet the criteria were classified into the CKD stages according to their first recorded outpatient serum creatinine measurement, and the index date was set to coincide with the measurement. However, if their initial eGFR fell below 60 ml/min/1.73 m^2 but did not meet the qualification criteria of sustaining eGFR <60 ml/min/1.73 m^2, they were placed under the eGFR category of ≥ 60ml/min/1.73 m^2. We ascertained proteinuria severity from the outpatient measurements of albumin-creatinine ratio

(ACR) and protein-creatinine ratio (PCR), as well as urine dipstick tests in the ± 6months from index date. Albuminuria was categorized based on the KDIGO definition as normal/mild (ACR < 3 mg/mmol, PCR < 15 mg/mmol, or UDIP negative / trace), moderate (ACR 3-30 mg/mmol, PCR 15-50 mg/mmol, UDIP 1+), severe (ACR ≥ 31 mg/mmol, PCR ≥ 51 mg/mmol, UDIP 2+ or higher) (4). Albumin-creatinine ratio was the primary measure of albuminuria used in the analysis, and if unavailable, was supplemented with PCR measurements. When both ACR and PCR were unavailable, dipstick urinalysis was used.

2.3. Ischemic heart disease: case definition

Standard case definitions for IHD and its components STEMI and NSTEMI are outlined in Table A.1. The case definition for IHD was adopted from the Canadian Chronic Disease Surveillance System (CCDSS) Heart Disease Working Group and case definitions of STEMI and NSTEMI were based on Scott et al.'s algorithm using ICD-10 codes, hospital discharge records, physician billing claims, and ambulatory care classification system (ACCS) files (39,40). These criteria were applied to patients who were 18 years of age or older. The date of diagnosis of IHD was the date of inpatient hospital separation or the last physician visit, whichever came first. The date of diagnosis of STEMI and NSTEMI was the date of hospital admission. The denominator for the rate and proportion calculations was the number of individuals in the provincial health registries (39).

2.4. Study outcomes

The burden (prevalence and incidence) IHD, STEMI and NSTEMI and the secular trends were evaluated using standard methods and stratified by kidney function status over the period 2003 to 2019. We excluded individuals that died or moved out of province during each year. The prevalence and incidence rates were standardized by age group and sex based on the 2011 Canadian population.

We assessed the quality of care based on the utilization of medications including aspirin, P2Y12 inhibitors, ACE inhibitors, ARBs, statins, SLGT2 inhibitors, and beta blockers within 6 months following diagnosis of STEMI and NSTEMI, and 12 months following the diagnosis of IHD. The usage of drugs was evaluated in a subgroup of individuals after January 2008, based on

the PIN drug file that was accessible. We performed a sensitivity analysis that was restricted to the patients diagnosed with IHD, STEMI and NSTEMI after the last PIN update, from January 1, 2013 (41). We also assessed whether patients achieved LDL levels below 2 mmol/L, urinary ACR levels below 3 mg/mmol and, for patients with diabetes, an HbA1c below 7%. LDL, HbA1c in diabetic patients and ACR levels were evaluated in individuals who had undergone at least one of these outpatient tests 12 months after being initially diagnosed with IHD and 6 months after being initially diagnosed with STEMI or NSTEMI. If there were multiple measurements, we utilized the first measurement. We assessed receipt of coronary artery perfusion by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) in the 6 months following diagnosis of STEMI or NSTEMI based on hospital discharge records, physician billing claims, and ACCS files (Table A.2).

2.5. Assessment of population demographic and clinical characteristics

We recorded baseline demographic data, including age, sex, and postal code of residence from the Alberta Health administrative data files. We linked postal codes to the Canadian Census using the Postal Code Conversion File (www.statcan.ca) to determine rural versus urban residential location. We assessed material deprivation based on the Pampalon Deprivation Index (1 = least deprived to 5 = most deprived) (42,43). We used ArcInfo software (version 10.0, ESRI) to determine the shortest distance by road between each patient's residence and the nearest nephrologist, as previously described (44,45). We delineated three categories for distance to nearest nephrology center: < 50 km, 50–100 km, and >100 km. Data were complete except for material deprivation index, rural or urban location, distance to nearest nephrology center (<2% missing); affected participants were assigned to a missing data category. We identified pre-existing co-morbid conditions from hospital discharge records, physician claims, and ambulatory care classification system files based on validated algorithms (46,47).

2.6. Statistical analysis

Continuous variables were summarized using medians and interquartile ranges since the data did not follow a normal distribution, and categorical variables were presented as proportions. Univariate least squares regression analysis and the negative binomial model were

used to determine the long-term pattern of the annual prevalence and the incidence rates of new cases from 2003 to 2019. Least squares regression offers a clear explanation of the temporal patterns present in the prevalence data, while using a negative binomial model for the incidence rates offers greater flexibility in the case of overdispersion. The prevalence and incidence rate were standardized by age group and sex weights based on the 2011 Canadian population. Each model included the year as a continuous variable. We did sensitivity analysis by using incorporating Newey–West standard error in the regression analysis to correct any autocorrelation of the regression (48). Each year corresponds to the period spanning from April 1 of the previous year to March 31 of that year (e.g., 2006 corresponds to April 1, 2005 to March 31, 2006). We analyzed the data using STATA version 18 and used $p < 0.05$ as the threshold for statistical significance.

Chapter 3.

Results

3.1. Baseline characteristics of the study cohort

Overall study population: data from a total of 3, 419,812 patients across all stages of kidney function between 2003 to 2019 were accessed (Table 3.1) for the selection of the study cohort.

Table 3.1. Total number of subjects in all CKD stages from 2003 to 2019.

CKD categories (ml/min/1.73m2/1.73m2)	N (%)
eGFR ≥ 60	3,123,966 (91.3%)
eGFR 45-59	235,301 (6.9%)
eGFR 30-44	48,503 (1.4%)
eGFR 15-29	10,605 (0.3%)
eGFR <15	1,437 (<0.1%)
Total	3,419,812

A total of 522, 961 patients with a history of ischemic heart disease and were included in our study cohort having met the inclusion criteria (Table 3.2). Included in the study cohort were 401,035 patients with an eGFR of ≥ 60 ml/min/1.73m^2, 93,600 patients with an eGFR of 45-59 ml/min/1.73m^2, 22,869 patients with an eGFR of 30-44 ml/min/1.73m^2, 4,958 patients with an eGFR of 15-29 ml/min/1.73m^2 and 499 patients with an eGFR of <15 ml/min/1.73m^2.

The average age of the cohort was 57.1 years with patients with eGFR of ≥ 60 ml/min/1.73 m² on average over 20 years younger than patients with eGFR <60 ml/min/1.73m^2. 43.8% of the cohort was female. Overall, 89.9% of patients lived in urban centers and 10.2% were from rural locations. There were no differences in material deprivation index and distance to the nearest nephrologist across all eGFRs. At baseline, relatively more patients with eGFRs <60 ml/min/1.73m^2 had moderate to severe proteinuria compared to patients with eGFR ≥ 60 ml/min/1.73m^2. Baseline HbA1c on average was 6.1% and was lower in patients with eGFR ≥ 60 ml/min/1.73m^2 (5.9%) compared to patients with eGFR ≥ 60 ml/min/1.73m^2. With respect to baseline comorbidities, relatively more patients with eGFR <60 ml/min/1.73m^2 had a history of myocardial infarction, diabetes, hypertension, previous PCI or CABG, peripheral arterial disease

and stroke compared to patients with eGFR ≥ 60 ml/min/1.73m^2. At baseline, relatively more patients with eGFR <60 ml/min/1.73m^2 had filled prescriptions for aspirin, P2Y12 inhibitors, dual antiplatelets, beta blockers, ACEi/ARBs, statins and SGLT2i compared to patients with eGFR ≥ 60 ml/min/1.73m^2 in the 12 months prior to enrollment in the cohort. For the cohort overall, the average number of patients that had filled prescriptions for these medications within the year prior to joining the study cohort were 18, 295 (11.3%), 4,377 (2.7%), 35, 402 (21.9%), 50, 718 (31.4%), 39, 559 (24.5%) and 485 (0.3%), respectively.

Table 3.2. Baseline characteristics of patients diagnosed with IHD between 2003 and 2019 by CKD stage.

	CKD stages by eGFR, ml/min/1.73m2/1.73m2					
	eGFR ≥ 60	**eGFR 45-59**	**eGFR 30-44**	**eGFR 15-29**	**eGFR <15**	**Total**
Number of subjects	401,035	93,600	22,869	4,958	499	522,961
Age, years	52.2 [43.1-62.1]	75.5 [68.3-81.7]	78.0 [70.7-84.0]	80.1 [72.2-85.7]	78.3 [68.7-84.3]	57.1 [46.1-70.9]
Female sex	167,436 (41.8)	45,862 (49.0)	12,533 (54.8)	2,898 (58.5)	254 (50.9)	228,983 (43.8)
Material Deprivation Index (scale 1 – 5)						
1	69,868 (17.4)	15,786 (16.9)	3,552 (15.5)	745 (15.0)	68 (13.6)	90,019 (17.2)
2	64,487 (16.1)	15,222 (16.3)	3,504 (15.3)	734 (14.8)	74 (14.8)	84,021 (16.1)
3	75,092 (18.7)	17,893 (19.1)	4,288 (18.8)	923 (18.6)	87 (17.4)	98,283 (18.8)
4	87,235 (21.8)	20,879 (22.3)	5,238 (22.9)	1,170 (23.6)	122 (24.4)	114,644 (21.9)
5	97,772 (24.4)	21,192 (22.6)	5,419 (23.7)	1,159 (23.4)	123 (24.6)	125,665 (24.0)
Missing	6,581 (1.6)	2,628 (2.8)	868 (3.8)	227 (4.6)	25 (5.0)	10,329 (2.0)
Location						
Urban	362,100 (90.3)	82,620 (88.3)	20,013 (87.5)	4,350 (87.7)	415 (83.2)	469,498 (89.8)
Rural	38,925 (9.7)	10,977 (11.7)	2,855 (12.5)	608 (12.3)	84 (16.8)	53,449 (10.2)
Missing	10 (0.0)	3 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	14 (0.0)
Distance to nearest nephrology center						
≤ 50 km	310,207 (77.4)	70,064 (74.9)	16,531 (72.3)	3,481 (70.2)	324 (64.9)	400,607 (76.6)
50–100 km	28,661 (7.1)	9,245 (9.9)	2,461 (10.8)	563 (11.4)	68 (13.6)	40,998 (7.8)
> 100 km	56,483 (14.1)	12,874 (13.8)	3,499 (15.3)	819 (16.5)	94 (18.8)	73,769 (14.1)
Missing	5,684 (1.4)	1,417 (1.5)	378 (1.7)	95 (1.9)	13 (2.6)	7,587 (1.5)
Proteinuria						
None/mild	249,791 (62.3)	49,918 (53.3)	10,244 (44.8)	1,713 (34.6)	116 (23.2)	311,782 (59.6)
Moderate	13,305 (3.3)	9,983 (10.7)	3,057 (13.4)	893 (18.0)	112 (22.4)	27,350 (5.2)
Severe	3,257 (0.8)	4,455 (4.8)	1,747 (7.6)	667 (13.5)	109 (21.8)	10,235 (2.0)
No urine protein measurements	134,682 (33.6)	29,244 (31.2)	7,821 (34.2)	1,685 (34.0)	162 (32.5)	173,594 (33.2)
HbA1C, %[c]	5.9 [5.5-6.8]	6.3 [5.8-7.2]	6.5 [5.9-7.4]	6.4 [5.9-7.3]	6.3 [5.9-7.0]	6.1 [5.6-7.0]

Comorbidities*						
Myocardial infarction	15,702 (3.9)	13,249 (14.2)	3,412 (14.9)	838 (16.9)	91 (18.2)	33,292 (6.4)
Diabetes	34,938 (8.7)	31,566 (33.7)	8,101 (35.4)	1,961 (39.6)	207 (41.5)	76,773 (14.7)
Hypertension	120,667 (30.1)	80,246 (85.7)	20,367 (89.1)	4,455 (89.9)	431 (86.4)	226,166 (43.2)
Previous PCI	14,607 (3.6)	13,038 (13.9)	2,598 (11.4)	500 (10.1)	58 (11.6)	30,801 (5.9)
Previous CABG	5,424 (1.4)	8,235 (8.8)	1,888 (8.3)	423 (8.5)	44 (8.8)	16,014 (3.1)
CAD	48,849 (12.2)	41,679 (44.5)	11,029 (48.2)	2,690 (54.3)	261 (52.3)	104,508 (20.0)
Peripheral arterial disease	2,879 (0.7)	5,066 (5.4)	1,466 (6.4)	392 (7.9)	37 (7.4)	9,840 (1.9)
Stroke/TIA	17,053 (4.3)	19,000 (20.3)	5,155 (22.5)	1,248 (25.2)	122 (24.4)	42,578 (8.1)
Cancer (non-metastatic)	8,149 (2.0)	7,238 (7.7)	1,763 (7.7)	379 (7.6)	61 (12.2)	17,590 (3.4)
Cancer (metastatic)	1,438 (0.4)	1,646 (1.8)	390 (1.7)	95 (1.9)	20 (4.0)	3,589 (0.7)
Lymphoma	698 (0.2)	1,031 (1.1)	219 (1.0)	53 (1.1)	13 (2.6)	2,014 (0.4)
Medication in the previous year**						
Number of patients for medication assessment	98,693	52,914	8,471	1,382	193	161,653
Aspirin	2,942 (3.0)	12,694 (24.0)	2,215 (26.1)	387 (28.0)	57 (29.5)	18,295 (11.3)
P2Y12	2,177 (2.2)	5,718 (10.8)	1,025 (12.1)	194 (14.0)	24 (12.4)	9,138 (5.7)
Dual antiplatelet	1,162 (1.2)	2,595 (4.9)	512 (6.0)	96 (6.9)	12 (6.2)	4,377 (2.7)
Anticoagulants	1,098 (1.1)	8,857 (16.7)	1,641 (19.4)	241 (17.4)	16 (8.3)	11,853 (7.3)
Beta blockers	5,857 (5.9)	24,472 (46.2)	4,288 (50.6)	696 (50.4)	89 (46.1)	35,402 (21.9)
Calcium channel blockers	2,447 (2.5)	14,721 (27.8)	2,570 (30.3)	481 (34.8)	40 (20.7)	20,259 (12.5)
ACEi/ARB	8,566 (8.7)	35,152 (66.4)	5,962 (70.4)	925 (66.9)	113 (58.5)	50,718 (31.4)
Diuretic	4,038 (4.1)	26,152 (49.4)	5,044 (59.5)	826 (59.8)	97 (50.3)	36,157 (22.4)
Statin	6,684 (6.8)	27,849 (52.6)	4,286 (50.6)	649 (47.0)	91 (47.2)	39,559 (24.5)
SGLT2i	26 (0.0)	406 (0.8)	49 (0.6)	2 (0.1)	2 (1.0)	485 (0.3)

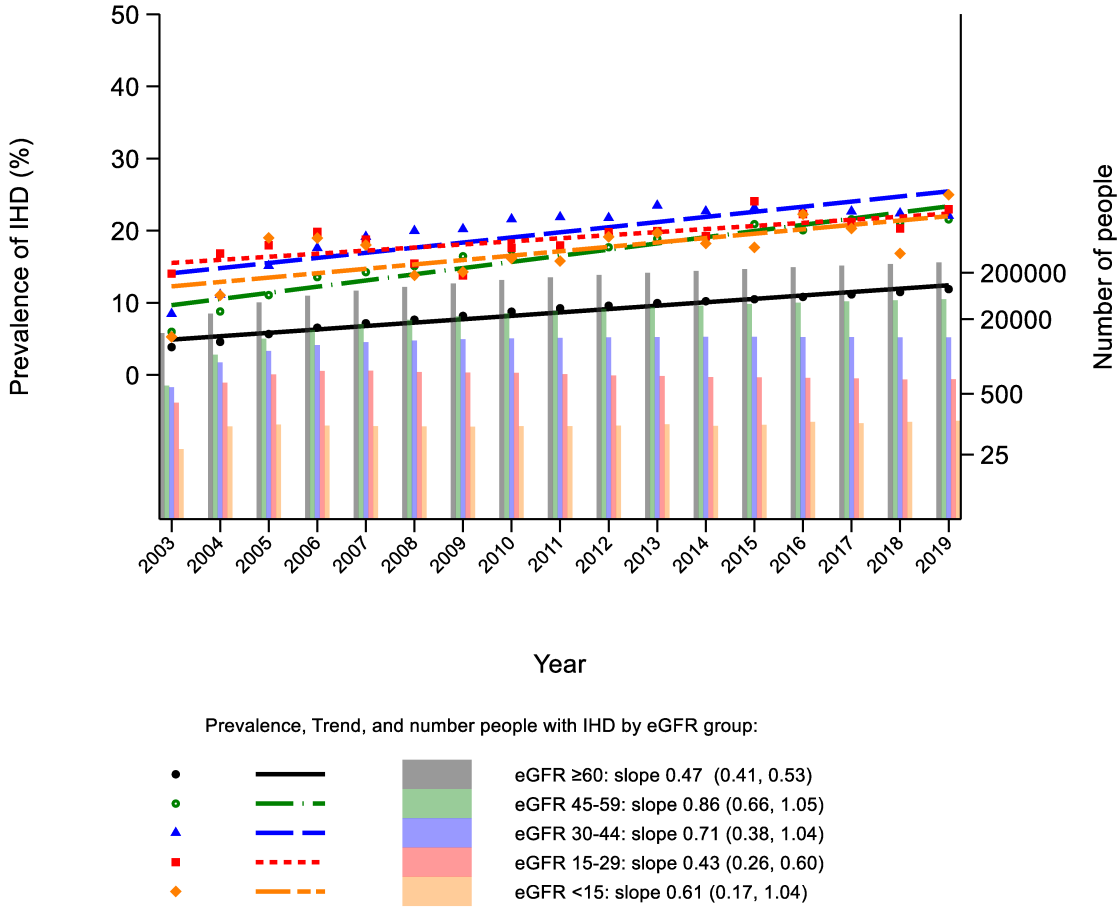
Data are presented as number (%) except for age, which are presented as median [interquartile range]. *Assessed by the presence of a diagnostic or procedural code from 1994 onwards to the index date except for cancer which are looked at 5-years back from index date, and CAD looked at 4-year back from CKD. **We looked at the baseline medications for the subjects whose index date of CKD was after January 1st, 2008. The Pharmaceutical Information Network (PIN) database provides patients' medication history since January 1st, 2008. SGLT2i has been available in Alberta since 2014. ***Media [IQR] was calculated based on 146,930 subjects had HbA1C measurements in the 6 months before and after index CKD date. Abbreviations: TIA, transient ischemic attack; ACEI/ARB,

angiotensin converting enzyme inhibitor/angiotensin receptor blocker; SGLT2i, sodium glucose cotransporter 2 inhibitor; HbA1C, hemoglobin A1C

3.2. Trend in the prevalence of ischemic heart disease in the study population

The age and sex standardized prevalence of IHD between 2003 and 2019 is depicted in Figure. 3.1 and Table B.1. The prevalence of IHD increased across all eGFRs from 2003 to 2019. In 2003, IHD had a prevalence of 3.9% or 9,949 patients with eGFR ≥ 60 ml/min/1.73m^2, 6.0% or 740 patients with eGFR 45-59 ml/min/1.73m^2, 8.5% or 688 patients with eGFR between 30-44 ml/min/1.73m^2, 14.0% or 319 patients with an eGFR between 15-29 ml/min/1.73m^2 and 5.3% or 32 patients with an eGFR <15 ml/min/1.73m^2. Compared to the prevalence of IHD in 2019 which was 11.9% or 331,876 patients with an eGFR ≥ 60 ml/min/1.73m^2, 21.6% or 53,538 patients with eGFR 45-59 ml/min/1.73m^2, 22.1% or 8,110 patients with eGFR 30-44 ml/min/1.73m^2, 23% or 1,026 patients with eGFR 15-29 ml/min/1.73m^2 and 25% or 130 patients with eGFR <15 ml/min/1.73m^2. The rates of change during this time were 0.86 (95% CI: 0.66, 1.05; p=<0.001), 0.71 (95% CI: 0.38, 1.04; p=0.159), 0.43 (95% CI: 0.26, 0.60; p=0.631) and 0.61 (95% CI: 0.17, 1.04; p=0.534), respectively (Table 3.3). Regression analysis of the annual rate of change from 2003 to 2019 showed that the prevalence of IHD increased across all eGFR categories with a significantly greater increase observed for patients with an eGFR 45-59 ml/min/1.73m^2 when compared to patients with an eGFR ≥ 60 ml/min/1.73m^2 (rate of change 0.86; 95% CI: 0.66, 1.05; p<0.001) (Table 3.3).

Figure 3.1. Prevalence of IHD by CKD stage between 2003 and 2019.



Each year corresponds to the period spanning from April 1 of the previous year to March 31 of that year (e.g., 2006 corresponds to April 1, 2005 to March 31, 2006). The prevalence was standardized by incorporating age group and sex weights based on the 2011 Canadian population (49).

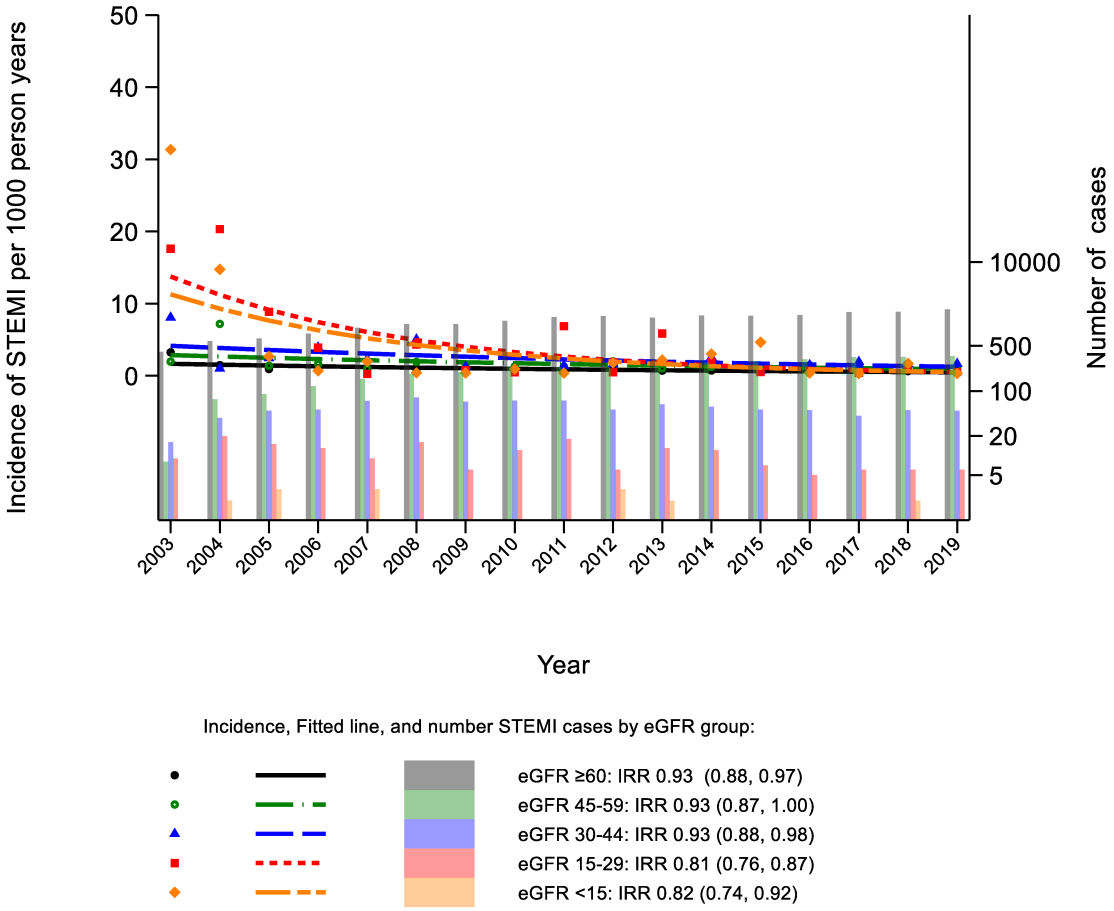
Table 3.3. Regression analysis for the annual rate of change in the prevalence of IHD from 2003 to 2019.

CKD Stage	Rate of change (95% CI)	Test for interaction
eGFR ≥ 60	0.47 (0.41, 0.53)	1 [Referent]
eGFR 45-59	0.86 (0.66, 1.05)	<0.001
eGFR 30-44	0.71 (0.38, 1.04)	0.159
eGFR 15-29	0.43 (0.26, 0.60)	0.631
eGFR <15	0.61 (0.17, 1.04)	0.534

3.3. Trends in the incidence and prevalence of STEMI

The age and sex standardized incidence of STEMI is depicted in Figure. 3.2 and in Table B.2. The incidence of STEMI decreased across all eGFRs from 2003 to 2019 except for patients with eGFR 45-59 ml/min/1.73m^2 (incidence risk ratio (IRR) of 0.93 (CI 95% 0.87, 1.00; p=0.885) (Table 3.4). In 2003, the incidence of STEMI was 3.2 per 1000 person years (404 cases) for patients with eGFR ≥ 60 ml/min/1.73m^2, 2 per 1000 person years (8 cases) for patients with eGFR 45-59 ml/min/1.73m^2, 8.1 per 1000 person years (16 cases) for patients with eGFR between 30-44 ml/min/1.73m^2, 17.6 per 1000 person years (9 cases) for patients with an eGFR between 15-29 ml/min/1.73m^2 and 31.4 (1 case) for patients with an eGFR <15 ml/min/1.73m^2. The incidence of STEMI for the cohort in 2019 was 0.7 per 1000 person years (1820 cases) for patients with an eGFR ≥ 60 ml/ min/ 1.73m^2, 1.2 per 1000 person years (346 cases) for patients with eGFR 45-59 ml/min/1.73m^2, 1.7 per 1000 person years (49 cases) for patients with eGFR 30-44 ml/min/1.73m^2, 0.5 per 1000 person years (6 cases) for patients with eGFR 15-29 ml/min/1.73m^2 and 0.3 per 1000 person years (1 case) for patients with eGFR <15 ml/min/1.73m^2. Compared to patients with eGFR ≥ 60 ml/min/1.73m^2, only patients with eGFR 15-29 ml/min/1.73m^2 had significantly greater decrease in the incidence of STEMI during this time (IRR: 0.81; CI 95%: 0.76, 0.87; p=0.004) (Table 3.4).

Figure 3.2. Age and sex standardized incidence of diagnosed STEMI by CKD stage between 2003 and 2019.



Each year corresponds to the period spanning from April 1st of the previous year to March 31st of that year (eg. 2006 corresponds to April 21st, 2005 to March 31st, 2006). The incidence rate was standardized by age group and sex weights based on the 2011 Canadian population.

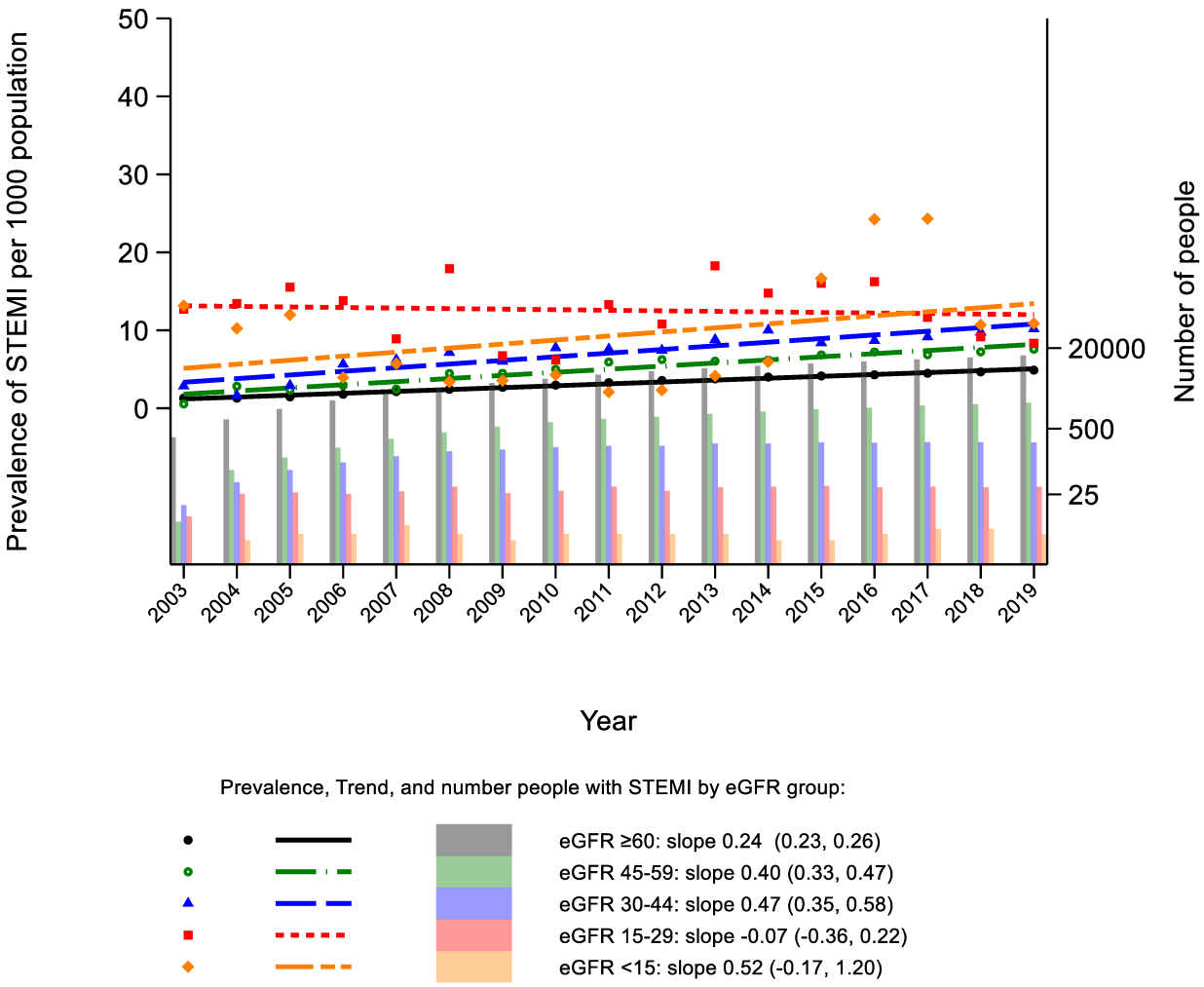
Table 3.4. Regression analysis for the annual incidence of STEMI from 2003 to 2019.

CKD Stage	Incidence Risk Ratio (95% CI)	Test for interaction
eGFR ≥ 60	0.93 (0.88, 0.97)	1 [Referent]
eGFR 45-59	0.93 (0.87, 1.00)	0.885
eGFR 30-44	0.93 (0.88, 0.98)	0.953
eGFR 15-29	0.81 (0.76, 0.87)	0.004
eGFR <15	0.82 (0.74, 0.92)	0.065

The age and sex standardized annual prevalence of STEMI between 2003 and 2019 is depicted Figure. 3.3 and in appendix B.3. The prevalence of STEMI increased for patients with eGFRs ≥ 30 ml/min/1.73m^2 from 2003 to 2019. When compared to patients with eGFR ≥ 60

ml/min/1.73m^2, statistically significant increases in the rate of change in the annual prevalence of STEMI were observed for patients with eGFR 45-59 ml/min/1.73m^2 (rate of change: 0.40; 95% CI: 0.33, 0.47; p=<0.001) and eGFR 30-44 ml/min/1.73m^2 (rate of change: 0.47; 95% CI: 0.35, 0.58; p=<0.001). A statistically significant decrease in the annual prevalence of STEMI was observed for patients with eGFR 15-29 ml/min/1.73m2 (rate of change -0.07; 95% CI: -0.36, 0.22; p=0.033). There was a non-significant increase during this time for patients with eGFR <15 ml/min/1.73m^2 (rate of change 0.52; 95% CI: -0.17, 1.20; p=0.424).

Figure 3.3. Age and sex standardized prevalence of diagnosed STEMI by CKD stage between 2003 and 2019.



Each year corresponds to the period spanning from April 1st of the previous year to March 31st of that year (eg.2006 corresponds to April 21st, 2005 to March 31st, 2006). The incidence rate was standardized by age group and sex weights based on the 2011 Canadian population.

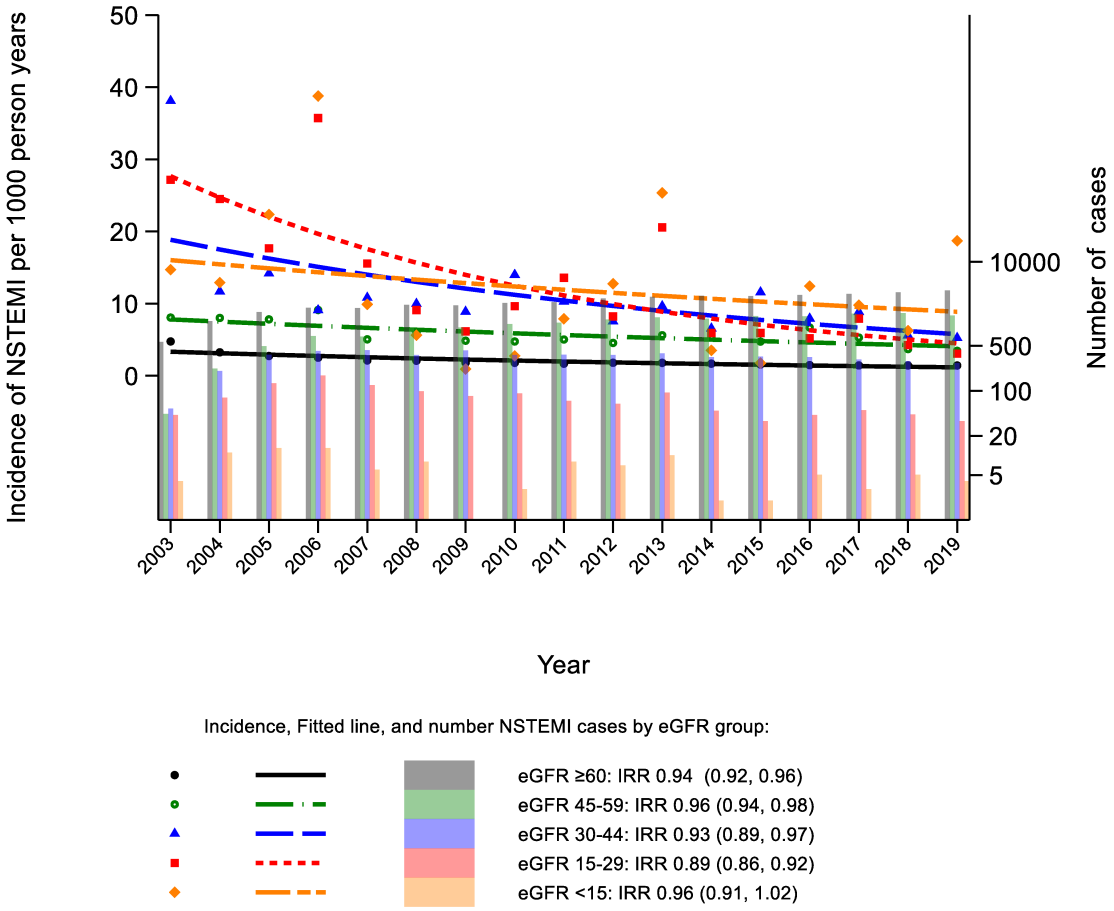
Table 3.5. Regression analysis for the annual prevalence of STEMI from 2003 to 2019.

CKD Stage	Rate of change (95% CI)	Test for interaction
eGFR ≥ 60	0.24 (0.23, 0.26)	1 [Referent]
eGFR 45-59	0.40 (0.33, 0.47)	<0.001
eGFR 30-44	0.47 (0.35, 0.58)	<0.001
eGFR 15-29	-0.07 (-0.36, 0.22)	0.033
eGFR <15	0.52 (-0.17, 1.20)	0.424

3.4. Trend in the incidence and prevalence of NSTEMI

The age and sex standardized annual incidence of NSTEMI is depicted in Figure. 3.4 and presented in Table B.4. The incidence of NSTEMI decreased across all eGFRs from 2003 to 2019 except for patients with an eGFR <15 ml/min/1.73m^2 (IRR: 0.96; CI 95%: 0.91, 1.02; p=0.376) (Table 3.6). In 2003, the incidence of NSTEMI was 4.8 per 1000 person years (571 cases) for patients with eGFR ≥ 60 ml/min/1.73m^2, 8.1 per 1000 person years (44 cases) for patients with eGFR 45-59 ml/min/1.73m^2, 38.1 per 1000 person years (53 cases) for patients with eGFR between 30-44 ml/min/1.73m^2, 27.2 per 1000 person years (42 cases) for patients with an eGFR between 15-29 ml/min/1.73m^2 and 14.7 (4 cases) for patients with an eGFR <15 ml/min/1.73m^2 (Table B.4). The incidence of NSTEMI for the cohort in 2019 was 1.4 per 1000 person years (3,576 cases) for patients with an eGFR ≥ 60 ml/min/1.73m^2, 3.5 per 1000 person years (1,468 cases) for patients with eGFR 45-59 ml/min/1.73m^2, 5.2 per 1000 person years (268 cases) for patients with eGFR 30-44 ml/min/1.73m^2, 3.1 per 1000 person years (34 cases) for patients with eGFR 15-29 ml/min/1.73m^2 and 18.7 per 1000 person years (4 case) for patients with eGFR <15 ml/min/1.73m^2 (Table B.4). Compared to patients with eGFR ≥ 60 ml/min/1.73m^2, only patients with eGFR 15-29 ml/min/1.73m^2 had significantly greater decrease in the incidence of NSTEMI during this time (IRR: 0.89; CI 95%: 0.86, 0.92; p=0.019) (Table 3.6).

Figure 3.4. Age and sex standardized incidence of diagnosed NSTEMI by CKD stage between 2003 and 2019.



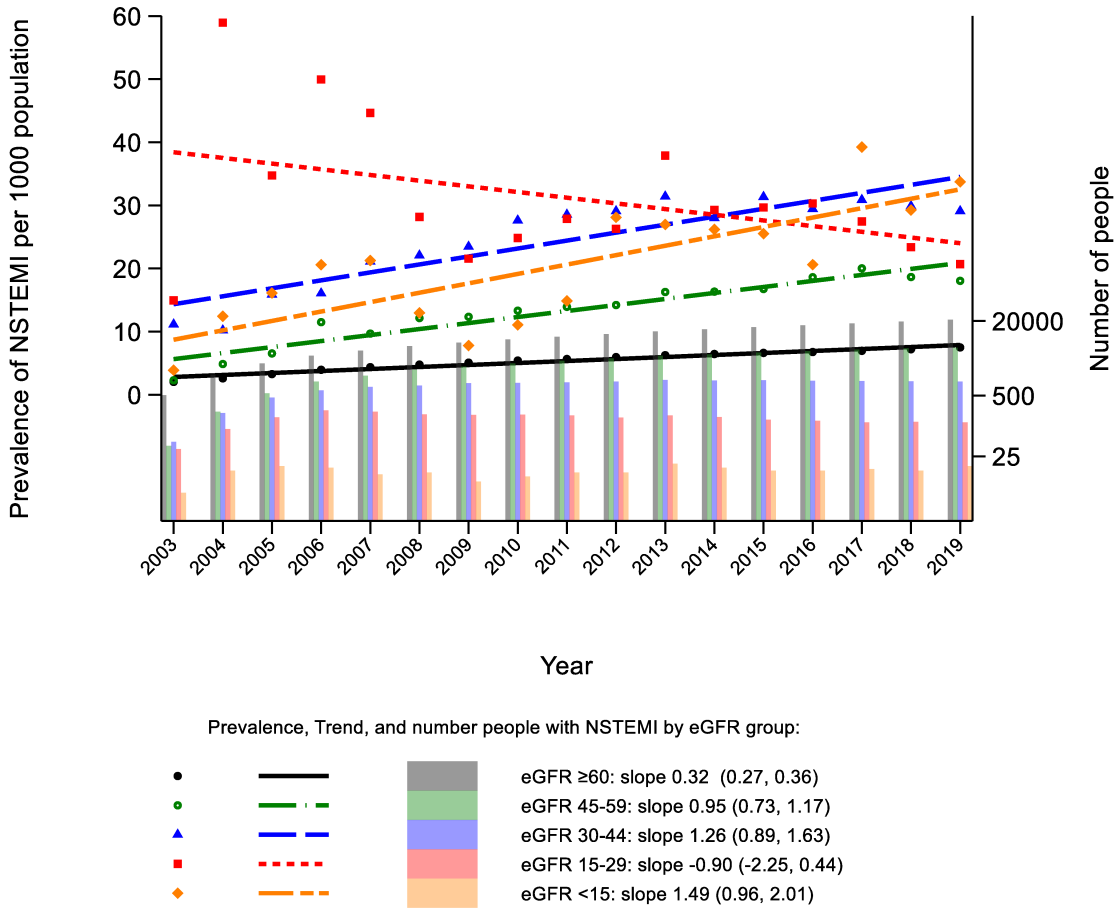
Each year corresponds to the period spanning from April 1st of the previous year to March 31st of that year (eg. 2006 corresponds to April 21st, 2005 to March 31st, 2006). The incidence rate was standardized by age group and sex weights based on the 2011 Canadian population.

Table 3.6. Regression analysis for the annual incidence of NSTEMI from 2003 to 2019.

CKD Stage	Incidence Risk Ratio (95% CI)	Test for interaction
eGFR ≥ 60	0.94 (0.92, 0.96)	1 [Referent]
eGFR 45-59	0.96 (0.94, 0.98)	0.078
eGFR 30-44	0.93 (0.89, 0.97)	0.750
eGFR 15-29	0.89 (0.86, 0.92)	0.019
eGFR <15	0.96 (0.91, 1.02)	0.379

The age and sex standardized annual prevalence of NSTEMI between 2003 and 2019 is depicted in Figure. 3.5 and Table B.5. The prevalence of NSTEMI increased for patients across all eGFRs except for patients with eGFR 15-29 ml/min/1.73m^2 (Table 3.7). When compared to patients with eGFR ≥ 60 ml/min/1.73m^2, statistically significant increases in the rate of change in the annual prevalence of NSTEMI were observed for patients with eGFR 45-59 ml/min/1.73m^2 (rate of change: 0.95; 95% CI: 0.73, 1.17; p<0.001), eGFR 30-44 ml/min/1.73m^2 (rate of change: 1.26; 95% CI: 0.89, 1.63; p<0.001) and eGFR <15 ml/min/1.73m^2 (rate of change: 1.49; 95% CI: 0.96, 2.01; p<0.001. There was a non-significant decrease in the annual prevalence in NSTEMI for patients with eGFR 15-29 ml/min/1.73m^2 (rate of change: -0.90; CI 95%: -2.25, 0.44; p<0.076).

Figure 3.5. Age and sex standardized prevalence of diagnosed NSTEMI by CKD stage between 2003 and 2019.



Each year corresponds to the period spanning from April 1st of the previous year to March 31st of that year (eg. 2006 corresponds to April 21st, 2005 to March 31st, 2006). The incidence rate was standardized by age group and sex weights based on the 2011 Canadian population.

Table 3.7. Regression analysis for the annual prevalence of NSTEMI from 2003 to 2019.

CKD Stage	Rate of change (95% CI)	Test for interaction
eGFR ≥ 60	0.32 (0.27, 0.36)	1 [Referent]
eGFR 45-59	0.95 (0.73, 1.17)	<0.001
eGFR 30-44	1.26 (0.89, 1.63)	<0.001
eGFR 15-29	-0.90 (-2.25, -0.44)	0.076
eGFR <15	1.49 (0.96, 2.01)	<0.001

3.5. Attainment of quality of care indicators

The quality of care received by patients within 12 months of diagnosis of ischemic heart disease was determined by identifying the proportion of patients that received pre-specified medications and met specific LDL, HbA1c and ACR guideline-recommended cut-offs. Table 3.8 depicts prescriptions filled 12 months after diagnosis of IHD for a sub-group of 381,744 patients that were diagnosed with IHD after January 2008 with PIN drug file data available. Results generally showed that, for patients with an eGFR of <60 ml/min/1.73m^2, the relative number of patients that filled prescriptions for ACEi/ARB and statins 12 months following diagnosis of IHD decreased as patient eGFR declined.

Overall, fewer patients with eGFR ≥ 60 ml/min/1.73m^2 filled prescriptions for ACEi/ARBs, statins, beta blockers and SGLT2i than patients with eGFR <60 ml/min/1.73m^2. 118,891 patients (40.4%) with an eGFR of ≥ 60 ml/min/1.73m^2 filled a prescription for ACEi/ARBs 12 months following diagnosis of IHD, compared to 114 (44.9%) with an eGFR of <15 ml/min/1.73m^2. Similarly, 113,183 (38.5%) of patients with eGFR ≥ 60 ml/min/1.73m^2 filled a prescription for a statin within 12 months following diagnosis of IHD compared to 131 (51.6%) of patients with an eGFR <15 ml/min/1.73m^2.

Fewer patients with eGFR ≥ 60 ml/min/1.73m^2 filled prescriptions for beta blockers compared to patients with eGFR <60 ml/min/1.73m^2 12 months following diagnosis of IHD and the relative number of patients filling prescriptions were similar for all patients with CKD. 77,542 patients (26.4%) with an eGFR ≥ 60 ml/min/1.73m^2 filled a prescription for a beta blocker 12 months following diagnosis of IHD, compared to 39, 362 (54.9%) with an eGFR of 45-59 ml/min/1.73m^2, 7,608 (56.6%) with an eGFR of 30-44 ml/min/1.73m^2, 1,156 (53.2%) with an eGFR of 15-29 ml/min/1.73m^2 and 132 (52%) of patients with an eGFR <15 ml/min/1.73m^2.

Overall, there were relatively few patients filling prescriptions for SGLT2i 12 months following diagnosis of IHD with 2,802 patients (1.0%) with an eGFR ≥ 60 ml/min/1.73m^2, 836 (1.2%) with an eGFR of 45-59 ml/min/1.73m^2, 85 (0.6%) with an eGFR of 30-44 ml/min/1.73m^2, 5 (0.2%) with an eGFR of 15-29 ml/min/1.73m^2 and 1 (0.4%) patient with an eGFR <15 ml/min/1.73m^2.

Table 3.8. Prescriptions filled within 12 months following diagnosis of IHD between 2008 and 2019.

	CKD categories (ml/min/1.73m2/1.73m2)					
	eGFR ≥ 60	**eGFR 45-59**	**eGFR 30-44**	**eGFR 15-29**	**eGFR <15**	**Number eligible patients‡**
ACEi/ARB	118,891 (40.4%)	49,070 (68.5%)	8,819 (65.6%)	1,192 (54.9%)	114 (44.9%)	381,744
Beta blockers	77,542 (26.4%)	39,362 (54.9%)	7,608 (56.6%)	1,156 (53.2%)	132 (52.0%)	381,744
SGLT2i	2,802 (1.0%)	836 (1.2%)	85 (0.6%)	5 (0.2%)	1 (0.4%)	381,744
Statin	113,183 (38.5%)	42,668 (59.6%)	7,317 (54.5%)	1,062 (48.9%)	131 (51.6%)	381,744

Results are presented as N (%) where N is the total number of patients and % is the percentage of the total. ‡The usage of drugs was evaluated in a subgroup of individuals who were initially diagnosed with IHD after January 2008, based on the PIN drug file that was accessible.

Data from the subgroup of patients with at least one outpatient laboratory value for LDL, HbA1c in patients with diabetes and urinary ACR within 12 months following the diagnosis of IHD between 2008 and 2019 are presented in Table 3.9. Results showed that, as eGFR declined, fewer patients achieved a urinary ACR of <3 mg/mmol 12 months following IHD. 39, 866 (81.6%) of patients with an eGFR ≥ 60 ml/min/1.73m^2 had a urinary ACR of <3 mg/mmol 12 months following IHD compared to 10, 518 patients (56.6%) with an eGFR 45-59 ml/min/1.73m^2, 1,830 patients (45.1%) with an eGFR 30-44 ml/min/1.73m^2, 247 patients (33.2%) with an eGFR 15-29 ml/min/1.73m^2 and 18 patients (27.7%) with an eGFR <15 ml/min/1.73m^2.

The percentage of patients with LDL <2 mmol/L 12 months after diagnosis of IHD was lower for patients with eGFR ≥ 60 ml/min/1.73m^2 compared to patients with eGFR <60 ml/min/1.73m^2. 62, 232 patients (31.3%) with an eGFR ≥ 60 ml/min/1.73m^2 had an LDL <2

mmol/L, compared to 21,800 patients (48.6%) with an eGFR 45-59 ml/min/1.73m^2, 4,218 patients (46.9%) with an eGFR 30-44 ml/min/1.73m^2, 736 patients (45.3%) with an eGFR 15-29 ml/min/1.73m^2 and 70 patients (47.9%) with an eGFR <15 ml/min/1.73m^2. Similarly, the percentage of diabetic patients with HbA1c <7% was lower in those with an eGFR ≥ 60 ml/min/1.73m^2 with 9,298 patients (41.3%) compared to patients with eGFR <60 ml/min/1.73m^2. However, as eGFR declined in patients with CKD, the number of patients obtaining HbA1c <7% increased with 10,667 patients (50.3%) with eGFR 45-59 ml/min/1.73m^2 obtaining an HbA1c <7%, 2,514 (50.5%) with an eGFR 30-44 ml/min/1.73m^2, 574 (53.3%) with an eGFR 15-29 ml/min/1.73m^2 and 66 (68.0%) with eGFR <15 ml/min/1.73m^2.

Table 3.9. LDL, HbA1c and urine ACR levels within 12 months following diagnosis of IHD between 2003 and 2019.

	CKD categories (ml/min/1.73m2/1.73m2)					
	eGFR ≥ 60	**eGFR 45-59**	**eGFR 30-44**	**eGFR 15-29**	**eGFR <15**	**Number eligible patients ‡**
LDL < 2 mmol/L	62,232 (31.3%)	21,800 (48.6%)	4,218 (46.9%)	736 (45.3%)	70 (47.9%)	254,575
HbA1C < 7%	9,298 (41.3%)	10,667 (50.3%)	2,514 (50.5%)	574 (53.3%)	66 (68.0%)	49,876
ACR <3 mg/mmol	39,866 (81.6%)	10,518 (56.6%)	1,830 (45.1%)	247 (33.2%)	18 (27.7%)	72,331

Results are presented as N (%) where N is the total number of patients and % is the percentage of the total. ‡LDL, HbA1C, ACR, and Total cholesterol levels were evaluated in individuals who had undergone at least one of these outpatient tests 12 months after being initially diagnosed with IHD. If there were multiple measurements, we utilized the first measurement.

3.6. Attainment of quality of care indicators for the management of STEMI

Results for the quality of care received by patients within 6 months of diagnosis of STEMI between 2003 and 2019 showed that overall, as eGFR declined, fewer patients received ACEi/ARBs, aspirin, beta blockers, P2Y12 inhibitors and statins 6 months following diagnosis of STEMI compared to patients with an eGFR ≥ 60 ml/min/1.73m^2 (Table 3.10). Furthermore, the number of patients filling prescriptions for aspirin within the 6 months following diagnosis of STEMI were low across all eGFRs with 8,002 (55.4%) of patients with eGFR ≥ 60 ml/min/1.73m^2 filling prescriptions, 1,344 (50.3%) with eGFR 45-59 ml/min/1.73m^2, 260

(45.9%) with eGFR 30-44 ml/min/1.73m^2, 34 (37.4%) with eGFR 15-29 ml/min/1.73m^2 and 8 (53.3%) with eGFR ml/min/1.73m^2.

Table 3.10. Prescriptions filled within 6 months following diagnosis of STEMI between 2008 and 2019.

	CKD categories (ml/min/1.73m2/1.73m2)					
	eGFR ≥ 60	**eGFR 45-59**	**eGFR 30-44**	**eGFR 15-29**	**eGFR <15**	**Number eligible patients‡**
ACEi/ARB	11,742 (81.3%)	1,867 (69.9%)	354 (62.5%)	60 (65.9%)	6 (40.0%)	17,787
Aspirin	8,002 (55.4%)	1,344 (50.3%)	260 (45.9%)	34 (37.4%)	8 (53.3%)	17,787
Beta blockers	11,558 (80.0%)	1,894 (70.9%)	366 (64.7%)	45 (49.5%)	7 (46.7%)	17,787
P2Y12 inhibitor	10,612 (73.5%)	1,594 (59.7%)	275 (48.6%)	38 (41.8%)	6 (40.0%)	17,787
Statin	12,048 (83.4%)	1,937 (72.5%)	361 (63.8%)	50 (54.9%)	8 (53.3%)	17,787

Results are presented as N (%) where N is the total number of patients and % is the percentage of the total. ‡The usage of drugs was evaluated in a subgroup of individuals who were initially diagnosed with STEMI after January 2008, based on the PIN drug file that was accessible.

Findings from the subgroup of patients with at least one outpatient laboratory value for LDL, HbA1c in patients with diabetes and urinary ACR levels within 6 months following the diagnosis of STEMI between 2003 and 2019 are presented in Table 3.11. Results showed that as eGFR declined, generally fewer patients obtained an LDL < 2 mmol/L and urinary ACR of <3 mg/mmol 6 months post STEMI. Of 11, 981 patients included in the subgroup, 8,099 (76.9%) patients with eGFR ≥ 60 ml/min/1.73m^2 had an LDL <2 mmol/L within 6 months following a STEMI compared to 874 patients (75.1%) with an eGFR of 45-59 ml/min/1.73m^2, 26 (72.2%) with an eGFR of 15-29 ml/min/1.73m^2 and 3 (50%) with an eGFR of <15 ml/min/1.73m^2. However, more patients with an eGFR of 30-44 ml/min/1.73m^2,185 (77.7%), had an LDL <2 mmol/L than those with an eGFR > 60 ml/min/1.73m^2.

As eGFR declined, fewer patients obtained an ACR of < 3 mg/mmol. Of 3, 075 patients included in the subgroup assessed for urinary, 2, 221 (85.9%) with an eGFR ≥ 60 ml/min/1.73m^2 had an ACR <3 mg/mmol 6 months following STEMI, compared to 201 (51.3%) with an eGFR

of 45-59 ml/min/1.73m^2, 29 (34.9%) with an eGFR of 30-44 ml/min/1.73m^2, 3 (25%) with an eGFR 15-29 ml/min/1.73m^2 and 0 patients with an eGFR of <15 ml/min/1.73m$_2$.

However, this trend was not observed for HbA1c in patients with diabetes. Results showed that the percentage of diabetic patients in the 6 months following STEMI with HbA1c <7% was lower in those with an eGFR ≥ 60 ml/min/1.73m^2, 340 patients (35.5%), compared to patients with eGFR <60 ml/min/1.73m^2. Relatively fewer patients with eGFR 45-59 ml/min/1.73m^2 obtained an HbA1c <7%, 206 (46.5%), compared to diabetic patients with eGFR 30-44 ml/min/1.73m^2, 63 (54.8%), eGFR 15-29 ml/min/1.73m^2, 8 (50.0%) and with eGFR <15 ml/min/1.73m^2, (50%).

Table 3.11. LDL, HbA1c and urine ACR levels within 6 months following diagnosis of STEMI between 2003 and 2019.

	CKD categories (ml/min/1.73m2/1.73m2)					
	eGFR ≥ 60	**eGFR 45-59**	**eGFR 30-44**	**eGFR 15-29**	**eGFR <15**	**Number eligible patients‡**
LDL < 2 mmol/L	8,099 (76.9%)	874 (75.1%)	185 (77.7%)	26 (72.2%)	3 (50.0%)	11,981
HbA1C < 7%	340 (35.5%)	206 (46.5)	63 (54.8)	8 (50.0)	2 (50.0)	1,536
ACR <3 mg/mmol	2,221 (85.9%)	201 (51.3%)	29 (34.9%)	3 (25.0%)	0 (0.0%)	3,075

Results are presented as N (%) where N is the total number of patients and % is the percentage of the total. ‡LDL, HbA1C, ACR, and Total cholesterol levels were evaluated in individuals who had undergone at least one of these outpatient tests 12 months after being initially diagnosed with IHD. If there were multiple measurements, we utilized the first measurement.

Table 3.12 presents the sub-group of 22,372 patients that were included to identify the number of patients receiving PCI or CABG within the 6 months following diagnosis of STEMI between 2003 and 2019. Results showed that as eGFR declined fewer patients received PCI or CABG and that there were low rates of CABG in the 6 months following diagnosis of STEMI. 13, 795 patients (76%) with eGFR ≥ 60 ml/min/1.73m^2 received PCI within 6 months following diagnosis of STEMI compared to 1,745 patients (54.5%) with an eGFR of 45-59 ml/min/1.73m^2, 359 (43.5%) with an eGFR of 30-44 ml/min/1.73m^2, 47 (28.1%) with an eGFR of 15-29 ml/min/1.73m^2 and 6 (23.1%) with an eGFR of <15 ml/min/1.73m^2. Similarly, 1,038 patients (5.7%) with an eGFR ≥ 60 ml/min/1.73m^2 underwent CABG, compared to 148 (4.0%) with an

eGFR of 45-59 ml/min/1.73m^2, 33 (4.0%) with an eGFR of 30-44 ml/min/1.73m^2, 1 (0.6%) with an eGFR 15-29 ml/min/1.73m^2 and 0 patients with an eGFR of <15 ml/min/1.73m^2.

Table 3.12. Number of patients receiving PCI or CABG 6 months following diagnosis of STEMI between 2003 and 2019.

	CKD categories (ml/min/1.73m2/1.73m2)					
	eGFR ≥ 60	**eGFR 45-59**	**eGFR 30-44**	**eGFR 15-29**	**eGFR <15**	**Number eligible patients**
CABG	1,038 (5.7%)	148 (4.6%)	33 (4.0%)	1 (0.6%)	0 (0.0%)	22,372
PCI	13,795 (76%)	1,745 (54.5%)	359 (43.5%)	47 (28.1%)	6 (23.1%)	22,372

Results are presented as N (%) where N is the total number of patients and % is the percentage of the total.

3.7. Attainment of guideline recommended quality of care indicators for the management of NSTEMI

Results for quality of care received by patients within 6 months of diagnosis of NSTEMI between 2003 and 2019 are presented in Table 3.13. Results showed that, overall, as eGFR declined, fewer patients received ACEi/ARBs, aspirin, beta blockers, P2Y12 inhibitors and statins 6 months following diagnosis of NSTEMI compared to patients with an eGFR ≥ 60 ml/min/1.73m^2 (Table 3.10). The number of patients filling prescriptions for aspirin within the 6 months following diagnosis of NSTEMI were low across all eGFRs with 11,752 (49%) of patients with eGFR ≥ 60 ml/min/1.73m^2 filling prescriptions for aspirin, 4,934 (46.1%) with eGFR 45-59 ml/min/1.73m^2, 1,183 (43%) with eGFR 30-44 ml/min/1.73m^2, 186 (39.1%) with eGFR 15-29 ml/min/1.73m^2 and 14 (31.1%) with eGFR ml/min/1.73m^2.

Table 3.13. Prescriptions filled within 6 months following diagnosis of NSTEMI between 2008 and 2019.

	CKD categories (ml/min/1.73m2/1.73m2)					
	eGFR ≥ 60	**eGFR 45-59**	**eGFR 30-44**	**eGFR 15-29**	**eGFR <15**	**Number eligible patients‡**
ACEi/ARB	17,027 (71.1%)	6,874 (64.2%)	1,515 (55.1%)	220 (46.2%)	18 (40.0%)	37,933
Aspirin	11,752 (49.0%)	4,934 (46.1%)	1,183 (43.0%)	186 (39.1%)	14 (31.1%)	37,933
Beta blockers	16,979 (70.9%)	7,046 (65.8%)	1,675 (61.0%)	265 (55.7%)	21 (46.7%)	37,933
P2Y12 inhibitor	13,481 (56.3%)	4,491 (42.0%)	943 (34.3%)	141 (29.6%)	13 (28.9%)	37,933
Statin	17,886 (74.6%)	6,868 (64.2%)	1,518 (55.2%)	250 (52.5%)	23 (51.1%)	37,933

Results are presented as N (%) where N is the total number of patients and % is the percentage of the total. ‡The usage of drugs was evaluated in a subgroup of individuals who were initially diagnosed with NSTEMI after January 2008, based on the PIN drug file that was accessible.

Findings from the subgroup of patients with at least one outpatient laboratory value for LDL, urinary ACR and, for patients with diabetes, an HbA1c within 6 months following the diagnosis of NSTEMI between 2003 and 2019 are presented in Table 3.14. Results generally showed that as eGFR declined fewer patients obtained an LDL < 2 mmol/L and ACR <3 mg/mmol 6 months post NSTEMI compared to patients with an eGFR ≥ 60 ml/min/1.73m^2. Of 18, 644 patients included in the subgroup, 10, 012 (71.2%) patients with eGFR ≥ 60 ml/min/1.73m^2 had an LDL <2 mmol/L within 6 months following an NSTEMI compared to 2, 461 patients (69.3%) with an eGFR of 45-59 ml/min/1.73m^2, 557 (64.6%) with an eGFR of 30-44 ml/min/1.73m^2 and 4 (57.1%) with an eGFR of <15 ml/min/1.73m^2.

Similarly, as eGFR declined, fewer patients obtained a urinary ACR < 3 mg/mmol. Of the 5,154 patients included in the subgroup looking at urinary ACR, 2,637 (78.8%), of patients with an eGFR ≥ 60 ml/min/1.73m^2 had an ACR <3 mg/mmol 6 months following NSTEMI, compared to 559 (41%) with an eGFR of 45-59 ml/min/1.73m^2, 127 (32.8%) with an eGFR of 30-44 ml/min/1.73m^2, 19 (35.2%) with an eGFR 15-29 ml/min/1.73m^2 and 0 patients with an eGFR of <15 ml/min/1.73m^2.

Overall, a similar trend was observed for HbA1c in patients with diabetes. Results showed that the percentage of diabetic patients with HbA1c <7% was higher in those with an

eGFR ≥ 60 ml/min/1.73m^2 5, 635 patients (74.3%), compared to patients with eGFR <60 ml/min/1.73m^2 in the 6 months following diagnosis of STEMI with 1, 993 (61.9%) obtaining HbA1c <7% with eGFR 45-59 ml/min/1.73m^2, 532 (62.6%) with eGFR 30-44 ml/min/1.73m^2 and 123 (66.5%) with eGFR 15-29 ml/min/1.73m^2. However, 10 (83.3%) of patients with eGFR <15 ml/min/1.73m^2 obtained HbA1c <7% in the 6 months following diagnosis of NSTEMI.

Table 3.14. LDL, HbA1c and urine ACR levels within 6 months following diagnosis of NSTEMI between 2003 and 2019.

	CKD categories (ml/min/1.73m2/1.73m2)					
	eGFR ≥ 60	**eGFR 45-59**	**eGFR 30-44**	**eGFR 15-29**	**eGFR <15**	**Number eligible patients‡**
LDL < 2 mmol/L	10,012 (71.2%)	2,461 (69.3%)	557 (64.6%)	100 (61.3%)	4 (57.1%)	18,644
HbA1C < 7%	5,635 (74.3%)	1,993 (61.9%)	532 (62.6%)	123 (66.5%)	10 (83.3%)	11,848
ACR <3 mg/mmol	2,637 (78.8%)	559 (41.0%)	127 (32.8%)	19 (35.2%)	0	5,154

Results are presented as N (%) where N is the total number of patients and % is the percentage of the total. ‡LDL, HbA1C, ACR, and Total cholesterol levels were evaluated in individuals who had undergone at least one of these outpatient tests 6 months after being initially diagnosed with NSTEMI. If there were multiple measurements, we utilized the first measurement.

Table 3.15 presents the sub-group of 49,688 patients that were used to identify the number of patients receiving PCI or CABG within the 6 months following diagnosis of NSTEMI between 2003 and 2019. Results showed that as eGFR declined fewer patients received CABG or PCI within then 6 months following diagnosis of NSTEMI. 13,163 patients (41.9%) with an eGFR ≥ 60 ml/min/1.73m^2 received PCI within 6 months following a NSTEMI compared to 2,569 (19.7%) with an eGFR of 45-59 ml/min/1.73m^2, 471 (11.%) with an eGFR of 30-44 ml/min/1.73m^2, 55 (5.7%) with an eGFR of 15-29 ml/min/1.73m^2 and 7 (7.8%) with an eGFR of <15 ml/min/1.73m^2. Similarly, 3, 210 patients (10.2%) with an eGFR ≥ 60 ml/min/1.73m^2 underwent CABG 6 months following an NSTEMI compared to 772 (5.9%) with an eGFR of 45-59 ml/min/1.73m^2, 174 (4.2%) with an eGFR of 30-44 ml/min/1.73m^2, 25 (2.6%) with an eGFR 15-29 ml/min/1.73m^2 and 3 patients (3.3%) with an eGFR of <15 ml/min/1.73m^2.

Table 3.15. Number of patients receiving PCI or CABG 6 months following diagnosis of NSTEMI between 2003 and 2019.

	CKD categories (ml/min/1.73m2/1.73m2)					
	eGFR ≥ 60	**eGFR 45-59**	**eGFR 30-44**	**eGFR 15-29**	**eGFR <15**	**Number eligible patients‡**
CABG	3,210 (10.2)	772 (5.9)	174 (4.2)	25 (2.6)	3 (3.3)	49,688
PCI	13,163 (41.9)	2,569 (19.7)	471 (11.4)	55 (5.7)	7 (7.8)	49,688

Results are presented as N (%) where N is the total number of patients and % is the percentage of the total.

3.8. Sensitivity analysis for medications received following diagnosis of IHD, STEMI and NSTEMI

The Alberta PIN was last updated in March 7th, 2012, so we conducted a sensitivity analysis that was restricted to patients diagnosed with IHD, STEMI and NSTEMI after January 1st, 2013 to identify the number of patients filling prescriptions for indicated medications. The results are presented in Appendix C (tables C.1 – C.3). Overall, the relative number of patients filling prescriptions for indicated medications increased across all eGFRs for all medications, but the same general trends were re-demonstrated, except for patients with eGFR <15. The number of patients filling prescriptions for indicated medications with eGFRs <15 increased after restricting the analysis to patients diagnosed with IHD after January 1st, 2013, however the numbers of these patients were relatively small, and were unlikely to be statistically significant.

Chapter 4.
Discussion

The goal of this work was to better understand the burden (prevalence and incidence) of IHD and changes over time among patients with CKD in Alberta. We have also examined receipt of guideline concordant care for IHD in this cohort with CKD across the spectrum of baseline kidney function. It has been well established that patients with CKD experience a greater morbidity and mortality from IHD than patients with normal kidney function and evidence suggests that patients with CKD and IHD may receive less invasive treatments and fewer medical therapies than the general population, possibly due to concern for side-effects and a more general conservative treatment approach towards CVD related care (6–8). However, there has been recent evidence suggesting a trend towards improvements in treatments and clinical outcomes in patients with CKD and IHD.

4.1. Summary of the findings for the trend in ischemic heart disease

We have found an increase in the prevalence of IHD across all eGFR categories from 2003 to 2019 whilst the annual incidence of STEMI decreased across all eGFR categories over the period, except for patients with eGFR 45-59 ml/min/1.73m^2. The annual prevalence of STEMI increased for patients with eGFRs ≥ 30 ml/min/1.73m^2 from 2003 to 2019. The incidence of NSTEMI decreased across all eGFRs from 2003 to 2019, except for patients with an eGFR <15 ml/min/1.73m^2 (IRR: 0.96; CI 95%: 0.91, 1.02; p=0.376). The prevalence of NSTEMI increased for patients across all eGFR categories except for patients with eGFR 15-29 ml/min/1.73m^2 which showed a decreasing trend over the period.

4.2. Summary of quality of care findings

The quality of care received by patients within 12 months of diagnosis of IHD and within the 6 months following diagnosis of STEMI and NSTEMI was determined by comparing the proportion of patients that received pre-specified medications, met specific LDL, HbA1c and ACR and received coronary revascularization to patients with normal kidney function. Results showed that in the 12 months following diagnosis of IHD, fewer patients with eGFR ≥ 60

ml/min/1.73m^2 filled prescriptions for ACEi/ARB, statins, and beta blockers than patients with eGFR <60 ml/min/1.73m^2 and that there were few prescriptions filled for SGLT2i overall. Furthermore, we found that for patients with an eGFR <60 ml/min/1.73m^2, the number of patients filling prescriptions for ACEi/ARB and statins 12 months following diagnosis of IHD decreased as patient eGFR declined. Similarly, as eGFR declined, fewer patients achieved a urinary ACR of <3 mg/mmol in the 12 months following diagnosis of IHD. However, we found the opposite trend for patients meeting LDL < 2 mmol/L and for patients with diabetes obtaining an HbA1c <7%, with relatively more patients with CKD obtaining these targets.

Furthermore, in the 6 months following diagnosis of STEMI, we found that as eGFR declined, fewer patients received ACEi/ARBs, aspirin, beta blockers, P2Y12 inhibitors and statins. Furthermore, overall prescriptions for aspirin were low across all eGFRs with 8,002 (55.4%) of patients filling prescriptions for aspirin with an eGFR ≥ 60 ml/min/1.73m^2, 1,344 patients (50.3%) with eGFR 45-59 ml/min/1.73m^2, 260 patients (45.9%) with eGFR 30-44 ml/min/1.73m^2, 34 patients (37.4%) with eGFR 15-29 ml/min/1.73m^2 and 8 patients (53.3%) with eGFR ml/min/1.73m^2. Results also showed that as eGFR declined fewer patients obtained a urinary ACR <3 mg/mmol or LDL < 2 mmol/L. Similarly to what was observed in patients with IHD, the relative number of patients with diabetes obtaining HbA1c <7% increasing as eGFR declined.

The results for the quality of care received by patients in the 6 months following diagnosis of NSTEMI were similar. As eGFR declined, fewer patients received ACEi/ARBs, aspirin, beta blockers, P2Y12 inhibitors and statins 6 months following diagnosis of NSTEMI and the number of patients filling prescriptions for aspirin was low across all eGFRs. Results also showed that, overall, as eGFR declined fewer patients obtained an LDL < 2 mmol/L, HbA1c <7% and ACR <3 mg/mmol. Finally, we found that as eGFR declined fewer patients received PCI or CABG in the 6 months following diagnosis of STEMI and NSTEMI.

4.3. Interpretation of findings

4.3.1. Trends in the burden of ischemic heart disease

Our results showed that the prevalence of IHD, NSTEMI and STEMI had increased over time which is in keeping with more patients living with these conditions and better access to

care. The overall number of prevalent cases of IHD has increased over time across all eGFR categories. Furthermore, there was a significantly greater increase in the prevalence for patients with eGFR 45-59 ml/min/1.73m^2 when compared to patients with an eGFR ≥ 60 ml/min/1.73m2 (rate of change 0.86; 95% CI: 0.66, 1.05; p<0.001).

Our results also showed that the annual prevalence of STEMI increased for patients with eGFRs ≥ 30 ml/min/1.73m^2 from 2003 to 2019 with a significantly greater increase in patients with eGFR 30-59 ml/min/1.73m^2 and a significantly greater decrease in patients with eGFR 15-29 ml/min/1.73m^2 when compared to patients with normal kidney function. Similarly, we found that the prevalence of NSTEMI increased for patients across all eGFRs except for patients with eGFR 15-29 ml/min/1.73m^2 which showed a decrease from 2003 to 2019 and that the increase was significantly greater for patients with eGFRs 30-59 ml/min/1.73m^2 and eGFR < 15 ml/min/1.73m^2. These results are consistent CCSDS data which showed a steady increase in prevalence of acute myocardial infarction from 2000 – 2001 from 1.18% (95% CI: 1.18-1.19) for both sexes to 1.97% (95% CI: 1.96–1.97) in 2020-2021 (40).

While we found that the prevalence of IHD has increased over time, we also found that the annual incidence of STEMI and NSTEMI has decreased from 2003 to 2019 in both patients with CKD and normal kidney function. This finding suggests that overall, patients, including those with CKD, are receiving better quality of care preventing the occurrence of acute coronary syndromes. Our findings are in line with the CCSDS data on incidence of myocardial infarction, which showed that it has decreased from 300 per 100, 000 in 2000-2001 (95% CI: 297-302) to 181 per 100, 000 (95% CI 180-182) in 2020-2021 with ongoing declining trend. This was associated with a declining trend in all-cause mortality rate within 365 days of acute myocardial infarction (11.77%; 95% CI: 10.80 – 13.04 in 2000-2001 for both sexes and 8.38% (95% CI 7.77-9.77) in 2020-2021 (40).

Our study not only showed a decline in the annual incidence of acute myocardial infarction over time, but we also found that some groups of patients with CKD may have had a greater rate of decrease than patients with normal kidney function. We found that the annual incidence of STEMI decreased across all eGFRs from 2003 to 2019, except for patients with eGFR 45-59 ml/min/1.73m^2. Compared to patients with eGFR ≥ 60 ml/min/1.73m^2, patients with eGFR 15-29 ml/min/1.73m^2 had significantly greater decrease in the incidence of STEMI during this time (IRR: 0.81; CI 95%: 0.76, 0.87; p=0.004). Furthermore, the incidence of NSTEMI

decreased across all eGFRs from 2003 to 2019 with exception of patients with an eGFR <15 ml/min/1.73m^2 (IRR: 0.96; CI 95%: 0.91, 1.02; p=0.376). Compared to patients with eGFR ≥ 60 ml/min/1.73m^2, patients with eGFR 15-29 ml/min/1.73m^2 had significantly greater decrease in the incidence of NSTEMI during this time (IRR: 0.89; CI 95%: 0.86, 0.92; p=0.019).

4.3.2. Quality of care in patients with chronic kidney disease and ischemic heart disease

Results for the quality of care received by patients with IHD and CKD showed that in general, more patients with CKD filled prescriptions for the indicated medications following IHD than patients with normal kidney function. We also found that the number of patients filling prescriptions with CKD declined as their eGFR declined. Furthermore, more patients with CKD and IHD filled prescriptions for statin therapy than patients with normal kidney function in the 12 months following diagnosis of IHD. Overall, fewer patients with eGFR eGFR ≥ 60 ml/min/1.73m^2 filled prescriptions for ACEi/ARB, statins, beta blockers than patients with eGFR <60 ml/min/1.73m^2. For example, we found that for patients with eGFR ≥ 60 ml/min/1.73m^2 only 40.4% filled a prescription for an ACEi/ARB, 26.4% for a beta blocker and 38.5% for a statin within the 12 months of diagnosis of IHD which was overall significantly lower than in patients with all stages of CKD.

A similar trend was found with a sensitivity analysis that was restricted to patients diagnosed with IHD after January 1st, 2013 to account for changes to the PIN data. We would have expected nearly all patients with IHD to have filled a prescription for a statin, regardless of kidney function, and the fact that the lowest number of prescriptions filled was for patients with normal kidney function is surprising. This finding may be, in part, explained by missing data and inherit flaws in using the PIN network data for clinical outcomes research. Another consideration is that patients with CKD would likely have other indications for receiving ACEi/ARBs and SGLT2is for example, and perhaps this explains in part why more patients with CKD and IHD filled prescriptions for these medications. Additionally, sensitivity analysis to identify comorbidities including hypertension, heart failure and diabetes would be helpful to better understand the discrepancy in the number of patients filling prescriptions for the specified medications.

Although, results for urinary ACR of <3 mg/mmol followed a general trend of fewer patients meeting this cut-off as eGFR declined, the opposite trend was observed for the relative number of patients with diabetes obtaining HbA1c <7% with relatively more patients with CKD obtaining this target as patient eGFR declined. Similarly, we found that only 31.3% of patients with IHD and an eGFR >60 ml/min/1.73m^2 had an LDL of <2 mmol/L. This was lower than in patients across all other eGFRs, with 48.6% meeting this cut-off with eGFR 45-59 ml/min/1.73m^2, 46.9% with eGFR 30-44 ml/min/1.73m^2, 45.3% with eGFR 15-29 ml/min/1.73m^2 and 47.9% with eGFR < 15 ml/min/1.73m^2. Taken together, these results suggest that patients with CKD are more frequently receiving appropriate statin therapy for secondary prevention as well as obtaining HbA1c targets more often compared to patients with IHD and normal kidney function.

4.3.3. Quality of care in patients with chronic kidney disease and STEMI or NSTEMI

Overall, our results suggested that the quality of care received by patients following STEMI and STEMI decreased as their eGFR declined. These findings are consistent with other registry studies, including Fox et al's study of 19,029 patients with diagnosed with STEMI and 30, 462 diagnosed with NSTEMI from the National Cardiovascular Data Registry Acute Coronary Treatment and Intervention Outcomes Network registry from January 1st 2007 to December 31st 2007 that included 280 hospitals. This study found that the risk of mortality increased with CKD stage and that, among patients presenting with STEMI, the odds ratio for any reperfusion therapy was significantly lower with worsening CKD (p=0.0005). Furthermore, patients with NSTEMI and CKD were less likely to undergo early invasive therapy (P<0.0001) or any revascularization (P<0.0002). The results also showed significantly lower rates of early in hospital aspirin use (P-trend <0.001 for STEMI and NSTEM) as well as use of clopidogrel, beta-blockers and statins (all p-trend <0.0001) in patients with more advanced CKD. This pattern was observed for these medication prescriptions at discharge as well (50).

Similarly, in our study we found that in the 6 months following diagnosis of STEMI and NSTEMI as patient eGFR declined, the relative number of patients filling prescriptions for indicated medications decreased and relatively fewer patients underwent PCI or CABG. In patients who were diagnosed with STEMI or NSTEMI, we found that as eGFR declined, fewer

patients received ACEi/ARBs, beta blockers, P2Y12 inhibitors and statins. However, unlike patients with IHD, more patients with eGFRs ≥ 60 ml/min/1.73m^2 filled prescriptions for these medications overall compared to patients with CKD. In the case of STEMI, 81.3% of patients filled a prescription for ACEi/ARB in the 6 months following diagnosis, 80% for beta blockers, 73.5% for P2Y12 inhibitors and 83.4% for statins. Across all medication classes, more prescriptions were filled in the 6 months following STEMI compared to NSTEMI.

We also found that, overall, the number of patients filling prescriptions for aspirin were low across all eGFRs in the 6 months following STEMI and NSTEMI. For example, within the 6 months following diagnosis of STEMI, 55.4% of patients with eGFR ≥ 60 ml/min/1.73m^2 filled prescriptions for aspirin, 50.3% with eGFR 45-59 ml/min/1.73m^2, 45.9% with eGFR 30-44 ml/min/1.73m^2, 37.4% with eGFR 15-29 ml/min/1.73m^2 and 53.3% with eGFR <15 ml/min/1.73m^2. Given that aspirin can be filled over the counter, the overall low percentage of prescriptions filled may be not reflect quality of care, but instead be the result of a limitation with using the Alberta's PIN.

Our results showed that there was low utilization of CABG in the 6 months following diagnosis of STEMI or NSTEMI across all eGFRs and as eGFR declined fewer patients underwent PCI or CABG. The rates of PCI in patients diagnosed with STEMI were 76% with eGFR ≥ 60 ml/min/1.73m^2, 54.5% with eGFR 45-59 ml/min/1.73m^2, 43.5% with eGFR 30-44 ml/min/1.73m^2, 28.1% with eGFR 15-29 ml/min/1.73m^2 and 23.1% with eGFR <15 ml/min/1.73m^2. The observed inverse relationship between eGFR and PCI may, in part, be due to a concern for contrast nephrotoxicity as well as a general more conservative approach towards patients with CKD.

The rates of PCI we observed were lower than have been observed from other studies of patients with CKD and STEMI. For example, Schmucker et al., (2022) using the Bremen STEMI-Registry, studied 9,605 STEMI-patients, 1018 with advanced CKD, between 2006 to 2019 and found that over time CKD-patients were more likely to be treated with PCI (2015-2019: 90.3% vs 2006-2010: 75.8%, p<0.01) and drug eluting stents (90.7% vs 1.3%, p<0.01) (23). They also found that both ticagrelor/prasugrel and drug eluting stents were associated with a decrease in ischemic events at 1 year with an increase in bleeding, but without a change in rate of acute kidney injury or 1 year mortality.

A similar decrease in utilization of PCI and CABG in patients with CKD within 6 months of diagnosis of NSTEMI was also observed. The overall trend was consistent with what has been observed in other cohorts (39,51). For example, Scott et al. studied a cohort of 5,385 patients hospitalized with acute myocardial infarction in the UK between 2015-2017 and found a reduced odds of invasive management in people with eGFR <60 ml/min/1.73m^2 compared with people with eGFR ≥60 ml/min/1.73m^2 when hospitalized for NSTEMI but not for STEMI (39). They hypothesized that their observation might be due to clinicians believing that the benefits of PCI in STEMI outweigh the risks posed to kidney function (39). Our cohort was larger, with 23,372 patients included who were diagnosed with STEMI and 49,688 who were diagnosed with NSTEMI, which may partially explain why we observed this inverse association.

Finally, we observed that, in the 6 months following diagnosis of STEMI or NSTEMI, as eGFR declined fewer patients obtained an LDL < 2 mmol/L and an ACR <3 mg/mmol. For example, in the 6 months following diagnosis of STEMI, the percentage of patients obtaining an LDL of <2 mmol/L were 76.9% with an eGFR ≥ 60 ml/min/1.73m^2, 75.1% with an eGFR 45-59 of ml/min/1.73m^2, 77.7% with an eGFR of 30-44 ml/min/1.73m^2, 72.2% with an eGFR of 15-29 ml/min/1.73m^2 and 50% with an eGFR <15 ml/min/1.73m^2. Patients diagnosed with NSTEMI had the same trend with slightly fewer patients meeting each laboratory target.

Although the results for urinary ACR of <3 mg/mmol and LDL <2 mmol/L within 6 months following diagnosis of STEMI followed a general trend of fewer patients meeting these cut-offs as eGFR declined, overall, the opposite trend was observed for the number of patients with diabetes obtaining HbA1c <7%. Relatively more patients with CKD obtained this target in the 6 months following diagnosis of STEMI. This pattern suggests that patients with CKD and a diagnosis of STEMI are more frequently obtaining HbA1c targets compared to patients with normal kidney function.

4.4. Key conclusions

- We found an increase in the prevalence of IHD from 2003-2019 for patients across all eGFR categories and a decrease in the incidence of STEMI and NSTEMI for some categories of CKD. This trend suggests that the background care for patients both with

and without CKD has improved over the past 20 years, leading to improved clinical outcomes.

- Compared to patients with normal kidney function, a greater proportion of patients with eGFR <60 ml/min/1.73m^2 attained the dyslipidemia target of LDL < 2 mmol/L within 12 months following the diagnosis of IHD. Furthermore, a greater proportion of patients with reduced kidney function and diabetes attained the glycemic target of HbA1c of 7% following the diagnosis of IHD and STEMI compared to patients with normal kidney function. Taken together, these results suggest that overall patients with reduced kidney are attaining recommended targets for markers of dyslipidemia and glycemic control.
- Compared to patients with normal kidney function, relatively fewer patients with eGFR <60 ml/min/1.73m^2 attained the dyslipidemia target of LDL < 2 mmol/L, HbA1c target of <7% and urinary ACR target of < 3 mg/mmol within 6 months following the diagnosis of NSTEMI.
- A greater proportion of patients with CKD filled prescriptions for indicated medications following diagnosis of IHD and a smaller proportion of patients with CKD filled prescriptions for these medications following the diagnosis of STEMI and NSTEMI when compared to patients with normal kidney function.
- Finally, patients with lower eGFRs generally received PCI and CABG less frequently in the 6 months following diagnosis of STEMI or NSTEMI. These findings highlight a significant opportunity for improving the quality of care in this patient population.

4.5. Strengths, limitations and future directions

The strength of this work is that for the first time, to our knowledge, we have established a large cohort using Alberta's robust province wide database to study the epidemiology and care received by patients with chronic kidney disease and ischemic heart over time disease in Alberta. There are several limitations with this study including limitations with respect to our data source, measured outcomes as well as those inherent in retrospective cohort studies. First, there are pitfalls with using the Alberta PIN data as over-the-counter drugs and non-prescription medications, such as aspirin, were not documented. This likely contributed to the observed lower numbers of patients filling prescriptions for this indicated medication. Future studies validating

using the Alberta PIN to collect data related to aspirin prescriptions could be done to validate this approach. Second, using the Alberta PIN data does not provide information regarding patient compliance with prescriptions. Third, the PIN offered limited data on SGLT2 inhibitors as these were made available in Alberta in 2014 and thus are underrepresented in our study cohort. Future studies should include more recent PIN profile data to include information on this class of medications. Fourth, we used eGFR measurements to categorize patients in our cohort according to their degree of kidney function, however, because not everyone in the general population will have had eGFR measurement data in the AKDN database, more patients with normal kidney function were likely not included in the analysis. Fifth, future studies should incorporate subgroup analysis, stratifying epidemiological trends by sex, as well as age and geographic location.

Finally, inherent in the use of ICD codes to define patient comorbidities and IHD is a lack of detailed clinical context surrounding these events. Furthermore, the treatment outcomes and patient response to interventions are not included in ICD codes. This highlights the importance of incorporating clinically relevant outcomes in future work, including cardiovascular disease related mortality data to better understand the impact that medications prescriptions as well as revascularisation post-acute coronary syndrome is having on long term outcomes in the chronic kidney disease population. Future studies, including prospective cohort studies, should look to establish a temporal association between interventions as clinically relevant outcomes that impact care. For example, prospective data could be used to evaluate progression to end stage kidney disease following coronary artery revascularization. Similar data could be used to understand the impact that anemia and bleeding events have on anti-platelet prescriptions following acute coronary events or the influence that potassium levels have on initiation of renin-angiotensin-aldosterone inhibition.

4.6. Conclusions

This study found that the prevalence of IHD increased from 2003-2019 for patients across all eGFR categories and a decrease in the incidence of STEMI and NSTEMI for some categories of CKD. We found that proportionally more patients with CKD attained the dyslipidemia therapeutic target of LDL < 2 mmol/L within 12 months following the diagnosis of

IHD compared to patients with normal kidney function. Furthermore, as kidney function declined proportionally more patients attained glycemic therapeutic target of HbA1c of 7% following the diagnosis of IHD and STEMI compared to patients with normal kidney function. Taken together, these results suggest that overall patients with CKD did receive recommended care over the study period.

A greater proportion of patients with CKD filled prescriptions for indicated medications following diagnosis of IHD when compared to patients with normal kidney function. The opposite was observed following the diagnosis of STEMI and NSTEMI with a smaller proportion of patients with CKD having filled prescriptions for indicated medications in the 6 months following diagnosis. Furthermore, patients with lower eGFRs generally received proportionally fewer PCI's and CABG. Future studies should better clarify the factors that mediate this association between eGFR and the management of IHD, STEMI and NSTEMI as well as look at the impact that this association has on cardiovascular disease related mortality and progression to end stage kidney disease.

This study shows a plateauing of the prevalence of IHD among the people living with CKD in Alberta, and this could suggest enhanced survival for IHD following high quality care. However, there remains significant opportunities for improving the quality of care for patients with CKD following acute coronary events, including STEMI and NSTEMI.

References

1. Sarnak MJ, Amann K, Bangalore S, Cavalcante JL, Charytan DM, Craig JC, et al. Chronic Kidney Disease and Coronary Artery Disease: JACC State-of-the-Art Review. J Am Coll Cardiol. 2019 Oct 8;74(14):1823–38.

2. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Hypertens Dallas Tex 1979. 2003 Nov;42(5):1050–65.

3. Szummer K, Lindhagen L, Evans M, Spaak J, Koul S, Åkerblom A, et al. Treatments and Mortality Trends in Cases With and Without Dialysis Who Have an Acute Myocardial Infarction: An 18-Year Nationwide Experience. Circ Cardiovasc Qual Outcomes. 2019 Sep;12(9):e005879.

4. Levin A, Stevens P, Bilous R, Coresh J, De Francisco A, De Jong P, et al. Kidney disease: Improving global outcomes (KDIGO) CKD work group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013 Jan;3(1):1–150.

5. London GM, Guérin AP, Marchais SJ, Métivier F, Pannier B, Adda H. Arterial media calcification in end-stage renal disease: impact on all-cause and cardiovascular mortality. Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc. 2003 Sep;18(9):1731–40.

6. Ishida JH, Johansen KL. Exclusion of Patients With Kidney Disease From Cardiovascular Trials. JAMA Intern Med. 2016 Jan 1;176(1):124.

7. Konstantinidis I, Nadkarni GN, Yacoub R, Saha A, Simoes P, Parikh CR, et al. Representation of Patients With Kidney Disease in Trials of Cardiovascular Interventions: An Updated Systematic Review. JAMA Intern Med. 2016 Jan;176(1):121–4.

8. Chertow GM, Normand SLT, McNeil BJ. "Renalism": Inappropriately Low Rates of Coronary Angiography in Elderly Individuals with Renal Insufficiency. J Am Soc Nephrol. 2004 Sep;15(9):2462–8.

9. Charytan D, Mauri L, Agarwal A, Servoss S, Scirica B, Kuntz, RE. The use of invasive cardiac procedures after acute myocardial infarction in long-term dialysis patients. Am Heart J. 2006 Sep;152(3):558–64.

10. Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, Jafar TH, Heerspink HJL, Mann JF, et al. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. The Lancet. 2013 Jul;382(9889):339–52.

11. Kottgen A, Russell SD, Loehr LR, Crainiceanu CM, Rosamond WD, Chang PP, et al. Reduced Kidney Function as a Risk Factor for Incident Heart Failure: The Atherosclerosis Risk in Communities (ARIC) Study. J Am Soc Nephrol. 2007 Apr;18(4):1307–15.

12. Abramson JL, Jurkovitz CT, Vaccarino V, Weintraub WS, Mcclellan W. Chronic kidney disease, anemia, and incident stroke in a middle-aged, community-based population: The ARIC Study. Kidney Int. 2003 Aug;64(2):610–5.

13. Wattanakit K, Folsom AR, Selvin E, Coresh J, Hirsch AT, Weatherley BD. Kidney Function and Risk of Peripheral Arterial Disease: Results from the Atherosclerosis Risk in Communities (ARIC) Study. J Am Soc Nephrol. 2007 Feb;18(2):629–36.

14. Astor BC, Coresh J, Heiss G, Pettitt D, Sarnak MJ. Kidney function and anemia as risk factors for coronary heart disease and mortality: The Atherosclerosis Risk in Communities (ARIC) Study. Am Heart J. 2006 Feb;151(2):492–500.

15. Alonso A, Lopez FL, Matsushita K, Loehr LR, Agarwal SK, Chen LY, et al. Chronic Kidney Disease Is Associated With the Incidence of Atrial Fibrillation: The Atherosclerosis Risk in Communities (ARIC) Study. Circulation. 2011 Jun 28;123(25):2946–53.

16. Van Der Velde M, Matsushita K, Coresh J, Astor BC, Woodward M, Levey AS, et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. Kidney Int. 2011 Jun;79(12):1341–52.

17. Hemmelgarn BR, Clement F, Manns BJ, Klarenbach S, James MT, Ravani P, et al. Overview of the Alberta Kidney Disease Network. BMC Nephrol. 2009 Dec;10(1):30.

18. Turin TC, Tonelli M, Manns BJ, Ravani P, Ahmed SB, Hemmelgarn BR. Chronic kidney disease and life expectancy. Nephrol Dial Transplant. 2012 Aug 1;27(8):3182–6.

19. Wakasugi M, Kazama JJ, Narita I. Mortality trends among Japanese dialysis patients, 1988–2013: a joinpoint regression analysis. Nephrol Dial Transplant. 2016 Sep;31(9):1501–7.

20. United States Renal Data System. 2023 USRDS Annual Data Report: Epidemiology of kidney disease in the United States. [Internet]. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2023. Available from: https://usrds-adr.niddk.nih.gov/2023/chronic-kidney-disease/3-morbidity-and-mortality-in-patients-with-ckd

21. Bagai A, Lu D, Lucas J, Goyal A, Herzog CA, Wang TY, et al. Temporal Trends in Utilization of Cardiac Therapies and Outcomes for Myocardial Infarction by Degree of Chronic Kidney Disease: A Report From the NCDR Chest Pain-MI Registry. J Am Heart Assoc. 2018 Dec 18;7(24):e010394.

22. Ocak G, Boenink R, Noordzij M, Bos WJW, Vikse BE, Cases A, et al. Trends in Mortality Due to Myocardial Infarction, Stroke, and Pulmonary Embolism in Patients Receiving Dialysis. JAMA Netw Open. 2022 Apr 18;5(4):e227624.

23.Schmucker J, Fach A, Osteresch R, Mata Marin LA, Retzlaff T, Rühle S, et al. Temporal trends in treatment strategies and clinical outcomes among patients with advanced chronic kidney disease and ST-elevation myocardial infarctions: results from the Bremen STEMI registry. BMC Cardiovasc Disord. 2022 Apr 1;22(1):142.

24.Patel B, Shah M, Dusaj R, Maynard S, Patel N. Percutaneous Coronary Intervention and Inpatient Mortality in Patients with Advanced Chronic Kidney Disease Presenting with Acute Coronary Syndrome. Bayl Univ Med Cent Proc. 2017 Oct 1;30(4):400–3.

25.Ford T, Corcoran D, Berry C. Stable coronary syndromes: pathophysiology, diagnostic advances and therapeutic need. Heart. 2018;104:284–92.

26.Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, et al. 2023 ESC Guidelines for the management of acute coronary syndromes. Eur Heart J. 2023 Oct 12;44(38):3720–826.

27.Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Ganiats TG, Holmes DR, et al. 2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014 Dec;130(25):2354–94.

28.Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth Universal Definition of Myocardial Infarction (2018). J Am Coll Cardiol. 2018 Oct 30;72(18):2231–64.

29.Virani SS, Newby LK, Arnold SV, Bittner V, Brewer LC, Demeter SH, et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. Circulation [Internet]. 2023 Aug 29 [cited 2024 Jan 6];148(9). Available from: https://www.ahajournals.org/doi/10.1161/CIR.0000000000001168

30.Anderson TJ, Grégoire J, Pearson GJ, Barry AR, Couture P, Dawes M, et al. 2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. Can J Cardiol. 2016 Nov;32(11):1263–82.

31.Kidney Disease: Improving Global Outcomes (KDIGO) Lipid Work Group. Kidney Disease: Improving Global Outcomes (KDIGO) Lipid Work Group. KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease. Kidney inter., Suppl. 2013; 3: 259–305. 3(Supplement):259–305.

32.McFarlane P, Cherney D, Gilbert R, Senior P. Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Managment of Diabetes in Canada: Chronic Kidney Disease in Diabetes. Can J Diabetes. 2018;42(Supp 1):S201–9.

33.Charytan DM, Wallentin L, Lagerqvist B, Spacek R, De Winter RJ, Stern NM, et al. Early angiography in patients with chronic kidney disease: a collaborative systematic review. Clin J Am Soc Nephrol CJASN. 2009 Jun;4(6):1032–43.

34.Huang HD, Alam M, Hamzeh I, Virani S, Deswal A, Aguilar D, et al. Patients with severe chronic kidney disease benefit from early revascularization after acute coronary syndrome. Int J Cardiol. 2013 Oct;168(4):3741–6.

35.Shaw C, Nitsch D, Lee J, Fogarty D, Sharpe CC. Impact of an Early Invasive Strategy versus Conservative Strategy for Unstable Angina and Non-ST Elevation Acute Coronary Syndrome in Patients with Chronic Kidney Disease: A Systematic Review. PloS One. 2016;11(5):e0153478.

36.Shavadia JS, Southern DA, James MT, Welsh RC, Bainey KR. Kidney function modifies the selection of treatment strategies and long-term survival in stable ischaemic heart disease: insights from the Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease (APPROACH) registry. Eur Heart J Qual Care Clin Outcomes. 2018 Oct 1;4(4):274–82.

37.Bangalore S, Maron DJ, O'Brien SM, Fleg JL, Kretov EI, Briguori C, et al. Management of Coronary Disease in Patients with Advanced Kidney Disease. N Engl J Med. 2020 Apr 23;382(17):1608–18.

38.Levey AS, Stevens LA, Schmid CH, Zhang Y (Lucy), Castro AF, Feldman HI, et al. A New Equation to Estimate Glomerular Filtration Rate. Ann Intern Med. 2009 May 5;150(9):604.

39.Scott J, Bidulka P, Taylor DM, Udayaraj U, Caskey FJ, Birnie K, et al. Management and outcomes of myocardial infarction in people with impaired kidney function in England. BMC Nephrol. 2023 Nov 2;24(1):325.

40. CCDSS Heart Disease Working Group. Heart Disease in Canada: Highlights from the Canadian Chronic Disease Surveillance System [Internet]. Ottawa: Public Health Agency of Canada; 2017 Jul. Available from: https://www.canada.ca/content/dam/phac-aspc/documents/services/publications/diseases-conditions/heart-disease-fact-sheet/heart-disease-factsheet-eng.pdf%EF%BB%BF.

41. Health Information Standards Committee for Alberta. Pharmaceutical Information Network Data Set [Internet]. Edmonton: Government of Alberta; 2012 Mar 2. Available from: https://open.alberta.ca/dataset/860f6056-2e73-4e19-9766-bf60ece3a3b5/resource/0d62420b-8b52-421e-afbb-7f88358fbc0a/download/pharmaceutical-data-standard-v2-1-2012-03-02.pdf.

42.Pampalon R, Raymond G. A deprivation index for health and welfare planning in Quebec. Chronic Dis Can. 2000;21(3):104–13.

43. Alberta Health Services. How to use the Pampalon deprivation index in Alberta [Internet]; 2016. Available from: https://ago-item-storage.s3.amazonaws.com/8df129ba3a5948d5a07f4e6c6215cd85/PampalonUserGuide2016.pdf.

44.Tonelli M, Manns B, Culleton B, Klarenbach S, Hemmelgarn B, Wiebe N, et al. Association between proximity to the attending nephrologist and mortality among patients receiving hemodialysis. Can Med Assoc J. 2007 Oct 23;177(9):1039–44.

45.Rucker D, Hemmelgarn BR, Lin M, Manns BJ, Klarenbach SW, Ayyalasomayajula B, et al. Quality of care and mortality are worse in chronic kidney disease patients living in remote areas. Kidney Int. 2011 Jan;79(2):210–7.

46.Tonelli M, Wiebe N, Fortin M, Guthrie B, Hemmelgarn BR, James MT, et al. Methods for identifying 30 chronic conditions: application to administrative data. BMC Med Inform Decis Mak. 2016 Jan;15(1):31.

47.Quan H, Khan N, Hemmelgarn BR, Tu K, Chen G, Campbell N, et al. Validation of a Case Definition to Define Hypertension Using Administrative Data. Hypertension. 2009 Dec;54(6):1423–8.

48.Newey WK, West KD. A Simple, Positive Semi-Definite, Heteroskedasticity and Autocorrelation Consistent Covariance Matrix. Econometrica. 1987 May;55(3):703.

49.Census Profile. 2011 Census. [Internet]. Toronto, Ontario (Code 3520005) and Ontario (Code 35) (table).; 2012 Oct. Report No.: Catalogue no. 98-316-XWE. Ottawa. Available from: http://www12.statcan.gc.ca/census-recensement/2011/dp-pd/prof/index.cfm?Lang=E (accessed September 9, 2024)

50.Fox CS, Muntner P, Chen AY, Alexander KP, Roe MT, Cannon CP, et al. Use of Evidence-Based Therapies in Short-Term Outcomes of ST-Segment Elevation Myocardial Infarction and Non–ST-Segment Elevation Myocardial Infarction in Patients With Chronic Kidney Disease: A Report From the National Cardiovascular Data Acute Coronary Treatment and Intervention Outcomes Network Registry. Circulation. 2010 Jan 26;121(3):357–65.

51.Bhatia S, Arora S, Bhatia SM, Al-Hijji M, Reddy YNV, Patel P, et al. Non–ST-Segment–Elevation Myocardial Infarction Among Patients With Chronic Kidney Disease: A Propensity Score–Matched Comparison of Percutaneous Coronary Intervention Versus Conservative Management. J Am Heart Assoc. 2018 Mar 20;7(6):e007920.

Appendix A

Table A.1. Case definitions of ischemic heart diasese (IHD), ST-elevation myocardial infarction (STEMI) and non-ST elevation myocardial infarction (NSTEMI)

Condition (age)	Case Definition	ICD* Codes	Data Source
IHD (18+)	At least one hospitalization OR Two physician billing claims (in any diagnosis filed). No restriction that the 2 claims must be found "within 1 year or less".	ICD-9: 410-414, 36.01, 36.02, 36.05, 36.10-36.19 ICD-10: I20-I25 ICD-9 to ICD-10 conversion: I20: 411. 413 I21: 410 I22: 410 I23: I24: 411 I25: 414, 412	Hospitalizations, physician billing claims from 1994 to 2019
STEMI/NSTEMI (18+)	**Prevalence:** At least 1 hospitalization listing a diagnostic code for STEMI in diagnostic sub-type M **Incidence:** At least 1 hospitalization (where hospitalization listing a diagnostic code for STEMI or NSTEMI in diagnostic types M, W, X, Y, 1, or 2	**STEMI:** ICD-10: I21.0, I21.1, I21.2, I21.3, I22.0, I22.1, I22.8 **NSTEMI:** ICD-10: I21.4, I21.9, I22.9	Hospitalizations from 1994 to 2019

*ICD = International Classification of Diseases; Type M = The one diagnosis or condition that can be described as being most responsible for the patient's stay in hospital; types W, X, Y = service transfer diagnosis type (W), (X), (Y) code associated with the first/second/third service transfer; Type 1 = condition that existed prior to admission, has been assigned an ICD-10-CA code, and satisfies the requirements for determining comorbidity; Type 2 = condition that arises post-admission, has been assigned an ICD-10- CA code and satisfies the requirements for determining comorbidity.

Table A.2. Case definitions of percutaenous coronary intervention (PCI) and coronary artery bypass grafting (CABG)

Condition	Case Definition	ICD* Codes	Data Source
PCI	At least one procedure/CCI[§] OR one CCP[‡‡] in any diagnosis field	CCI: 1IJ50, 1IJ54GQ-AZ, 1IJ57GQ ICD*-9-CM[†] (procedure): 0066, 3601, 3602, 3603, 3605, 3606 CCP: 51.59C, 51.59D, 51.59E, 51.59F, 48.02, 48.03	Hospitalizations, physician billing claims, ACCS from 1994 to 2019 (except ACCS which begins in 1997)
CABG	At least one procedure/CCI[§] OR one CCP[‡‡] in any diagnosis field	CCI: 1IJ76 ICD-9-CM (procedure): 361, 362 CCP: 48.11, 48.12, 48.13, 48.14, 48.15, 48.19,	Hospitalizations, physician billing claims, ACCS from 1994 to 2019 (except ACCS which begins in 1997)

*ICD = International Classification of Diseases; § CCI = Canadian Classification of Health Interventions; ‡‡CCP = Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures; † CM = Clinical Modification; ACCS = Ambulatory Care Classification System

Appendix B

Table B.1. Prevalence (% and number) of diagnosed IHD by CKD stage from 2003 to 2019.

	Prevalence of IHD (%)					**Number of people with IHD**				
Year	eGFR ≥60	eGFR 45-59	eGFR 30-44	eGFR 15-29	eGFR <15	eGFR ≥60	eGFR 45-59	eGFR 30-44	eGFR 15-29	eGFR <15
2003	3.9	6.0	8.5	14.0	5.3	9949	740	688	319	32
2004	4.6	8.8	11.1	16.8	11.0	26408	3438	2353	865	98
2005	5.7	11.1	15.1	18.0	19.0	45690	7540	4114	1286	108
2006	6.5	13.6	17.6	19.8	19.0	63884	11780	5535	1537	102
2007	7.2	14.2	19.2	18.7	18.0	81261	15577	6350	1565	100
2008	7.7	15.1	20.0	15.4	13.8	98899	19439	6887	1460	99
2009	8.2	16.5	20.2	13.8	14.3	117512	22979	7382	1422	97
2010	8.8	17.3	21.6	17.6	16.2	138381	26771	7703	1393	100
2011	9.2	17.7	21.9	17.9	15.8	158418	30024	7904	1304	100
2012	9.6	17.7	21.8	19.8	19.1	177407	33132	8062	1220	102
2013	10.0	18.9	23.5	19.9	19.7	197511	36403	8257	1202	109
2014	10.2	18.9	22.7	19.3	18.2	217374	39232	8289	1131	101
2015	10.5	20.9	23.1	24.1	17.7	238281	42350	8339	1119	107
2016	10.8	20.1	22.7	22.3	22.3	260787	45355	8249	1090	123
2017	11.2	21.6	22.7	21.2	20.3	283159	48266	8184	1057	115
2018	11.5	21.1	22.4	20.3	16.8	306440	50896	8103	1006	124
2019	11.9	21.6	22.1	23.0	25.0	331876	53538	8110	1026	130

Table B.2. Incidence (per 1000 popoulation and number) of diagnosed STEMI by CKD stage from 2003 to 2019.

	Incidence of STEMI per 1000 person years					**Number of STEMI cases**				
Year	eGFR ≥60	eGFR 45-59	eGFR 30-44	eGFR 15-29	eGFR <15	eGFR ≥60	eGFR 45-59	eGFR 30-44	eGFR 15-29	eGFR <15
2003	3.2	2.0	8.1	17.6	31.4	404	8	16	9	1
2004	1.5	7.2	1.0	20.3	14.7	587	74	38	20	2
2005	0.9	1.4	2.5	8.9	2.7	650	89	49	15	3
2006	0.9	1.6	3.9	3.9	0.7	770	118	51	13	1
2007	0.9	1.0	2.3	0.3	2.0	951	152	70	9	3
2008	0.9	1.9	5.0	4.3	0.4	1080	183	79	16	1
2009	0.8	1.3	1.2	0.8	0.4	1079	194	68	6	1
2010	0.8	1.3	2.8	0.5	0.9	1206	238	71	12	1
2011	0.9	1.3	1.4	6.9	0.4	1380	235	71	18	1
2012	0.8	2.0	1.6	0.5	1.8	1440	224	51	6	3
2013	0.7	1.0	1.8	5.9	2.2	1361	248	62	13	2
2014	0.7	1.2	2.6	1.9	3.0	1465	275	57	12	1
2015	0.7	1.2	0.7	0.5	4.7	1454	290	51	7	1
2016	0.6	1.5	1.5	0.7	0.4	1498	309	50	5	1
2017	0.7	1.1	1.9	0.4	0.3	1660	332	41	6	1
2018	0.6	1.3	1.6	0.9	1.7	1670	337	50	6	2
2019	0.7	1.2	1.7	0.5	0.3	1820	346	49	6	1

Table B.3. Prevalence (per 1000 popoulation and number) of diagnosed STEMI by CKD stage from 2003 to 2019.

	Prevalence of STEMI per 1000 population					**Number of people with STEMI**				
Year	eGFR ≥60	eGFR 45-59	eGFR 30-44	eGFR 15-29	eGFR <15	eGFR ≥60	eGFR 45-59	eGFR 30-44	eGFR 15-29	eGFR <15
2003	1.3	0.6	2.8	12.7	13.2	336	7	15	9	1
2004	1.3	2.8	1.6	13.4	10.2	763	75	43	25	3
2005	1.5	2.3	2.9	15.5	12.0	1225	132	75	27	4
2006	1.8	2.9	5.7	13.8	4.0	1809	207	106	25	4
2007	2.1	2.5	6.2	8.9	5.7	2522	312	140	28	6
2008	2.4	4.5	7.2	17.9	3.4	3265	420	175	35	4
2009	2.7	4.5	6.0	6.7	3.6	4024	542	191	26	3
2010	3.0	5.0	7.8	6.2	4.3	4874	671	214	29	4
2011	3.3	5.9	7.6	13.3	2.1	5866	774	226	35	4
2012	3.6	6.2	7.4	10.8	2.3	6879	862	227	29	4
2013	3.8	6.0	8.8	18.3	4.2	7836	974	251	34	4
2014	4.0	6.2	10.0	14.8	6.0	8853	1087	253	35	3
2015	4.1	6.9	8.4	16.0	16.7	9809	1205	263	36	3
2016	4.3	7.2	8.7	16.2	24.2	10804	1305	262	34	4
2017	4.5	6.9	9.1	11.7	24.3	11878	1426	268	35	5
2018	4.7	7.2	9.8	9.2	10.7	12990	1523	266	34	5
2019	4.9	7.6	10.2	8.4	10.9	14214	1621	265	35	4

Table B.4. Incidence (per 1000 popoFor ulation and number) of diagnosed NSTEMI by CKD stage from 2003 to 2019.

	Incidence of NSTEMI per 1000 person years					**Number of NSTEMI cases**				
Year	eGFR ≥60	eGFR 45-59	eGFR 30-44	eGFR 15-29	eGFR <15	eGFR ≥60	eGFR 45-59	eGFR 30-44	eGFR 15-29	eGFR <15
2003	4.8	8.1	38.1	27.2	14.7	571	44	53	42	4
2004	3.2	8.0	11.7	24.5	12.9	1201	221	202	79	11
2005	2.7	7.8	14.2	17.7	22.4	1658	492	363	131	13
2006	2.5	9.1	9.1	35.7	38.8	1920	706	415	173	13
2007	2.1	5.0	10.8	15.6	9.9	1906	693	425	122	6
2008	2.1	5.9	10.0	9.1	5.6	2147	924	360	98	8
2009	1.8	4.9	8.9	6.1	0.9	2093	950	419	83	1
2010	1.8	4.7	14.0	9.6	2.7	2294	1084	358	91	3
2011	1.7	5.0	10.3	13.6	7.9	2346	1135	362	70	8
2012	1.8	4.5	7.5	8.2	12.8	2691	1269	359	63	7
2013	1.8	5.6	9.6	20.6	25.4	2843	1364	381	94	10
2014	1.7	5.3	6.6	5.9	3.5	2942	1308	333	49	2
2015	1.6	4.7	11.6	5.9	1.8	2939	1441	340	34	2
2016	1.5	6.7	7.9	5.2	12.4	3033	1419	331	42	5
2017	1.4	5.3	8.8	7.9	9.8	3174	1558	306	50	3
2018	1.4	3.7	5.6	4.2	6.2	3332	1601	287	43	5
2019	1.4	3.5	5.2	3.1	18.7	3576	1468	268	34	4

Table B.5. Prevalence (per 1000 popoulation and number) of diagnosed NSTEMI by CKD stage from 2003 to 2019.

	Prevalence of NSTEMI per 1000 population					**Number of people with NSTEMI**				
Year	eGFR ≥60	eGFR 45-59	eGFR 30-44	eGFR 15-29	eGFR <15	eGFR ≥60	eGFR 45-59	eGFR 30-44	eGFR 15-29	eGFR <15
2003	2.0	2.3	11.1	15.0	3.9	506	41	50	35	4
2004	2.6	4.9	10.2	58.9	12.4	1403	223	208	94	12
2005	3.3	6.5	15.9	34.7	16.1	2444	557	450	168	15
2006	3.9	11.5	16.1	49.9	20.6	3579	993	645	239	14
2007	4.4	9.7	21.1	44.6	21.3	4604	1321	766	224	10
2008	4.8	12.1	22.1	28.2	13.0	5728	1763	816	196	11
2009	5.1	12.3	23.5	21.6	7.8	6799	2082	915	190	7
2010	5.4	13.3	27.6	24.8	11.1	7976	2448	929	193	9
2011	5.6	13.9	28.5	27.9	14.9	9116	2789	955	186	11
2012	6.0	14.2	29.1	26.3	28.1	10450	3138	989	166	11
2013	6.3	16.3	31.4	37.9	27.0	11874	3540	1069	186	17
2014	6.4	16.3	28.0	29.3	26.2	13269	3837	1051	172	14
2015	6.6	16.7	31.3	29.7	25.5	14674	4167	1053	150	12
2016	6.8	18.6	29.4	30.3	20.6	16087	4474	1031	142	12
2017	7.0	20.0	30.9	27.5	39.2	17597	4849	1020	132	13
2018	7.2	18.6	29.9	23.4	29.3	19315	5148	1007	135	12
2019	7.5	18.0	29.1	20.7	33.7	21164	5301	994	131	15

Appendix C

Table C.1. Prescriptions filled within 12 months following diagnosis of IHD between 2013 and 2019.

	CKD categories (ml/min/1.73m2/1.73m2)					
	eGFR ≥ 60	**eGFR 45-59**	**eGFR 30-44**	**eGFR 15-29**	**eGFR <15**	**Number eligible patients‡**
ACEi/ARB	11,314 (35.3%)	17,527 (72.0%)	2,581 (70.9%)	327 (53.3%)	49 (55.7%)	60,724
Beta blockers	8,417 (26.3%)	14,951 (61.5%)	2,425 (66.6%)	377 (61.4%)	58 (65.9%)	60,724
SGLT2i	437 (1.4%)	729 (3.0%)	71 (2.0%)	4 (0.7%)	1 (1.1%)	60,724
Statin	11,166 (34.8%)	16,358 (67.2%)	2,401 (65.9%)	360 (58.6%)	57 (64.8%)	60,724

Results are presented as N (%) where N is the total number of patients and % is the percentage of the total. ‡The usage of drugs was evaluated in a subgroup of individuals who were initially diagnosed with IHD after January 1st, 2013, based on the PIN drug file that was accessible.

Table C.2. Prescriptions filled within 6 months following diagnosis of STEMI between 2013 and 2019

	CKD categories (ml/min/1.73m2/1.73m2)					
	eGFR ≥ 60	**eGFR 45-59**	**eGFR 30-44**	**eGFR 15-29**	**eGFR <15**	**Number eligible patients‡**
ACEi/ARB	5,960 (84.4%)	934 (71.8%)	132 (63.5%)	21 (67.7%)	4 (57.1%)	8,608
Aspirin	4,103 (58.1%)	676 (52.0%)	99 (47.6%)	14 (45.2%)	5 (71.4%)	8,608
Beta blockers	5,857 (82.9%)	951 (73.1%)	143 (68.8%)	15 (48.4%)	5 (71.4%)	8,608
P2Y12 inhibitor	5,763 (81.6%)	875 (67.3%)	118 (56.7%)	16 (51.6%)	6 (85.7%)	8,608

Results are presented as N (%) where N is the total number of patients and % is the percentage of the total. ‡The usage of drugs was evaluated in a subgroup of individuals who were initially diagnosed with STEMI after January 1st, 2013, based on the PIN drug file that was accessible.

Table C.3. Prescriptions filled within 6 months following diagnosis of NSTEMI between 2013 and 2019

	CKD categories (ml/min/1.73m2/1.73m2)					
	eGFR ≥ 60	**eGFR 45-59**	**eGFR 30-44**	**eGFR 15-29**	**eGFR <15**	**Number eligible patients‡**
ACEi/ARB	7,688 (73.2%)	2,895 (65.4%)	501 (56.7%)	51 (37.8%)	9 (50%)	15,963
Aspirin	5,413 (51.5%)	2,040 (46.1%)	384 (43.4%)	46 (34.1%)	7 (38.9%)	15,963
Beta blockers	7,587 (72.2%)	2,968 (67.1%)	557 (63.0%)	79 (58.5%)	9 (50%)	15,963
P2Y12 inhibitor	6,700 (63.8%)	2,059 (46.5%)	357 (40.4%)	44 (32.6%)	8 (44.4%)	15,963

Results are presented as N (%) where N is the total number of patients and % is the percentage of the total. ‡The usage of drugs was evaluated in a subgroup of individuals who were initially diagnosed with NSTEMI after January 1st, 2013, based on the PIN drug file that was accessible.