QUALITY OF PRIMARY CARE FOR CHRONIC KIDNEY DISEASE

UNDERSTANDING AND IMPROVING THE QUALITY OF PRIMARY CARE FOR PATIENTS WITH CHRONIC KIDNEY DISEASE

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LAY ABSTRACT

Chronic kidney disease is a medical condition where a person's kidney function is permanently reduced. Family doctors are responsible for the care of patients with early chronic kidney disease. However, many patients may not be receiving the right treatments from their family doctors to keep their kidneys healthy. This research used Ontario healthcare data to identify care gaps for patients with early chronic kidney disease. Interviews were then done with family doctors to identify reasons for one of these care gaps; specifically, why doctors do not always repeat blood and urine tests to confirm if patients have chronic kidney disease. Finally, this research looked at whether providing certain treatments led to better patient outcomes. This information can be used to update current guidelines and to inform strategies which help patients with chronic kidney disease receive the best possible care.

ABSTRACT

Background: International guidelines provide recommendations for early chronic kidney disease care. This thesis was completed to 1) measure the quality of chronic kidney disease care and identify gaps, 2) identify reasons why patients do not receive recommended care, and 3) determine if these guideline-recommended practices are associated with better patient outcomes.

Methods: Population-based cohort studies were conducted for studies 1, 3 and 4. Using consensus-based indicators, study 1 quantified the quality of care for patients with early chronic kidney disease. Study 2 was a qualitative descriptive study eliciting primary care physicians' perceived enablers and barriers to follow-up laboratory testing to confirm chronic kidney disease. Study 3 assessed the association between non-steroidal anti-inflammatory drug (NSAID) use versus non-use and adverse clinical outcomes among older adults. Study 4 assessed whether routine serum creatinine and potassium monitoring (versus no monitoring) following angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) initiation among older adults associated with better outcomes.

Results: In study 1, most recommendations were being followed; however, some care gaps were identified. For example, half of the patients with initial abnormal kidney test results did not receive follow-up tests. This finding prompted study 2, where enablers and barriers to this practice were identified. Providers were aware that they should be ordering follow-up tests and had the resources to do so. However, some providers perceived this practice as low priority. In study 3, NSAID use was associated with a higher risk of

complications. In study 4, routine ACEi / ARB monitoring did not prevent adverse outcomes.

Conclusions: This thesis provides a better understanding of care gaps for patients with early chronic kidney disease in Ontario, and reasons for one of these care gaps. This research also provides evidence to help strengthen guideline recommendations (NSAID avoidance) or refute them (ACEi / ARB monitoring).

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LIST OF ABBREVIATIONS

List of Abbreviations used:

ACE, Angiotensin Converting Enzyme

ACEi, Angiotensin Converting Enzyme Inhibitor

ACR, Albumin-to-Creatinine Ratio

ADG, Aggregated Diagnosis Groups

AKI, Acute Kidney Injury

ARB, Angiotensin Receptor Blocker

CCI, Canadian Classification for Health Interventions

CI, Confidence Interval

CIHI, Canadian Institute for Health Information

CKD, Chronic Kidney Disease

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration formula

DAD, Discharge Abstract Database

eGFR, estimated Glomerular Filtration Rate

EMR, Electronic Medical Record

Kidney Disease Improving Global Outcomes (KDIGO)

KP, Kaiser Permanente

KPNC, Kaiser Permanente Northern California

HR, Hazard Ratio

ICD-10, 10th edition of the Canadian Modified International Classification of Disease system

ICES, Institute for Clinical Evaluative Sciences

IQR, Interquartile Range

KDIGO, Kidney Disease Improving Global Outcomes

LOESS, Locally Weighted Scatterplot Smoothing

NACRS, National Ambulatory Care Reporting System

NSAIDs, Non-steroidal Anti-inflammatory Drugs

OLIS, Ontario Laboratories Information System

OR, Odds Ratio

ORN, Ontario Renal Network

RAAS, Renin-Angiotensin-Aldosterone System

SCr, Serum Creatinine

SD, Standard Deviation

Stan. Diff., Standardized Difference

TDF, Theoretical Domains Framework

TCPS2, Tri-Council Policy Statement 2

DECLARATION OF ACADEMIC ACHIEVEMENT

I declare that I led each of the four studies in this thesis throughout my doctoral training (2013 – 2018), with the co-authors providing supervision or a supportive role as indicated below for each study.

Study 1

I developed the initial study and analysis plan with oversight by my supervisor (AXG). I completed the initial literature review of previous studies. KT led the Delphi Panel to develop the quality indicators. KSB, MMR and EM provided input and approved the study and analysis plan. I completed all data programming and statistical analyses, with some guidance from EM. All authors helped interpret the results. I drafted the initial manuscript and all other authors critically reviewed and revised the manuscript. All authors reviewed and approved the final manuscript.

Study 2

AXG, KSB, MMR and I were responsible for study conception. My committee member (MMR) and I were responsible for the study design. I performed background literature searches, conducted all the interviews, and completed the analysis of the transcripts, with oversight by MMR. AXG and KSB provided feedback on the study design and findings. I drafted the initial manuscript with help from MMR. All authors reviewed and approved of the manuscript.

Study 3

I developed the initial study and analysis plan with oversight by AXG. KSB, MMR, EM, JCF, PR, and MAW provided input and approved of the study and analysis plan. I completed all data programming and statistical analyses, with some guidance from EM. All authors helped with interpretation of the results. PR created the online calculator. I drafted the initial manuscript with some help from AXG, and all other authors critically reviewed and revised the manuscript. All authors reviewed and approved the final manuscript.

Study 4

I developed the initial study and analysis plan with oversight by AXG and AG. All other authors provided input and approved of the study and analysis plan. RP completed all analyses for the Kaiser component and I completed all analyses for the Ontario component, with some guidance from EM. All authors helped with interpretation of the results. I drafted the initial manuscript with some help from AXG, and all other authors critically reviewed and revised the manuscript. All authors reviewed and approved the final manuscript.

1. INTRODUCTION

1.1 Background

More than 4 million of the 36 million people in Canada (12.5%) are living with chronic kidney disease,[1] which is characterized by a sustained reduction in kidney function that can progress to kidney failure or death. Patients who reach kidney failure and need renal replacement therapy (dialysis or kidney transplantation) are among the highest cost users of the Ontario healthcare system, with per-patient total healthcare costs approaching $100,000 per year, and all-patient healthcare costs of $830 million per year.[2] Unfortunately, patients with kidney failure generally have a worse prognosis than patients with cancer.[3] From 2005 to 2015, chronic kidney disease attributable deaths increased by 32%, with a total of 1.2 million deaths from chronic kidney disease in 2015 worldwide.[4]

Early detection of chronic kidney disease allows physicians to provide appropriate management to help prevent or slow the progression to kidney failure. Approximately 90% of patients with chronic kidney disease are in the early stages (i.e., stages 1-3b),[1] and are cared for by primary care providers.[5,6] Patients are typically referred to nephrologists when they reach the later stages of chronic kidney disease, or demonstrate features that suggest they are at a higher risk of progressive kidney disease. International guidelines published in 2013 from Kidney Disease Improving Global Outcomes (KDIGO) provide clinicians with evidence-based recommendations for the appropriate identification, evaluation and management of patients with chronic kidney disease.[7]

KDIGO recommends that chronic kidney disease be diagnosed based on serum creatinine tests to estimate the glomerular filtration rate (eGFR; the rate at which the

kidneys filter blood and remove wastes) and urine albumin-to-creatinine (ACR) tests, which measure the amount of protein in the urine.[7] Chronic kidney disease is identified by eGFR levels below 60 mL/min/1.73m^2 or urine ACR above 3 mg/mmol.[7] Individuals with first evidence of these laboratory markers should receive repeat measurements to confirm a diagnosis.[7]

Patients with chronic kidney disease should receive regular serum creatinine and urine ACR tests to monitor their kidney function.[7] Based on KDIGO recommendations, patients should also receive prescription medications to help prevent cardiovascular disease and/or slow their kidney disease progression, including a statin,[8,9] and either an angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blockers (ARBs) (use of both an ACEi and ARB together is contraindicated).[10–13] Although ACEi and ARBs are beneficial with long-term use, they can cause short-term complications such as acute kidney injury (a rapid reduction in kidney function) and hyperkalemia (clinically high levels of serum potassium).[11,14,15] These complications can result in major cardiovascular events, kidney failure, or death.[14,16–20] Therefore, guidelines recommend that patients with chronic kidney disease have their serum creatinine and serum potassium measured shortly after initiating an ACEi or an ARB.[7,21,22] Furthermore, guidelines also recommend that patients with chronic kidney disease should avoid medications that may aggravate kidney dysfunction, such as non-steroidal anti-inflammatory drugs (NSAIDs)[7,21,23] which may cause acute kidney injury and hyperkalemia.[24–26]

Although the guidelines are targeted at nephrologists, primary care providers may be less aware of these guidelines. There have been initiatives in several jurisdictions to

help bridge this gap in primary care. For example, the Ontario Renal Network (ORN), the provincial agency responsible for the delivery of kidney care services in Ontario, released an algorithm based on these clinical guidelines to aid primary care providers with appropriate screening, monitoring, management, and referral for chronic kidney disease (the KidneyWise toolkit).[27,28]

Measuring adherence to evidence-based guidelines is commonly done to assess the quality of care.[29] In order to measure guideline adherence among primary care providers, Dr. Tu et al. (2017) led a modified Delphi panel to develop a consensus set of quality indicators for early chronic kidney disease care.[30] These indicators included screening tests for disease recognition, routine laboratory monitoring to assess disease progression, and appropriate use of medications.

1.2 Problem Statement

Patients with early chronic kidney disease should receive the best possible care from their primary care provider to avoid disease progression and complications. There are no previous population-based studies in Ontario describing the quality of care provided to patients with early chronic kidney disease. Having a better understanding of current care practices can help identify care gaps and areas for attention. For example, qualitative studies can explore reasons for low adherence to certain guideline-recommended care practices. It is also important to verify that following these recommended care practices actually improves patient outcomes. Some of the guideline recommendations for chronic kidney disease care are based on poor-quality evidence, where no clinical trials or well-conducted population-based studies have ever been

completed. For example, there is high-quality evidence that ACEi or ARBs cause acute kidney injury or hyperkalemia,[11,12] but little evidence that laboratory monitoring after initiation of these drugs prevents major adverse clinical outcomes .[31,32] Similarly, there are population-based studies showing that high dose NSAIDs versus low dose are associated with a higher risk of accelerated kidney function decline among patients with chronic kidney disease.[33,34] However, there are no population-based cohort studies showing that NSAID use versus non-use increases the risk of serious complications for patients with chronic kidney disease, since the evidence is primarily limited to case-control studies.[24] Performing population-based cohort studies using administrative healthcare data can help provide better evidence, especially for care practices where a clinical trial is not expected to be conducted (due to ethical or logistical barriers, such as inability to claim clinical equipoise or the need for very large samples for adequate statistical power).

1.3 Study Objectives and Research Questions

The objectives of this thesis were:

1) to identify gaps in early chronic kidney disease care,
2) to understand why some recommendations are not being implemented in practice, and
3) to determine if following guideline-recommended practices for chronic kidney disease is associated with improved clinical outcomes.

Four related studies were completed to address these objectives with the following research questions:

- Study 1: What proportion of patients with chronic kidney disease in Ontario are receiving appropriate care based on a consensus-set of quality of care indicators?
- Study 2: Among primary care providers in Ontario, what are the perceived enablers and barriers to patients receiving follow-up laboratory tests after initial abnormal kidney function is detected?
- Studies 3 and 4: Is following guideline-recommended practices for early chronic kidney disease care associated with better clinical outcomes? Specifically:
    - Among older adults, is prescription NSAID use (>14 day supply) versus no prescription NSAID use associated with higher 30-day risk of acute kidney injury and hyperkalemia? Which NSAID users are at highest risk of these outcomes?
    - Among older adults initiating an ACEi or ARB, does routine laboratory monitoring versus no monitoring reduce the risk of 30-day all-cause mortality, hospitalization with acute kidney injury, and hospitalization with hyperkalemia?

1.4 Research Overview

Using a retrospective cohort design, the first study provided an overview of the quality of care received for patients with early chronic kidney disease in Ontario between 2006 and 2012. This study informed the remaining three studies. In particular, we found the following care gaps among patients with chronic kidney disease in Ontario:

1) 50% did not receive repeat laboratory testing after an initial abnormal serum creatinine or urine ACR test result;

2) 16% received at least one course of prescription NSAIDs with a day supply of more than 14 days;
3) 75% did not have their serum creatinine and potassium checked in the 7 to 30 days after initiating an ACEi or ARB.

To explore the first care gap finding, a qualitative descriptive study was conducted with primary care providers (physicians and nurse practitioners) in Ontario who cared for patients with chronic kidney disease. This study summarized the perceived enablers and barriers to performing repeat laboratory tests after an initial abnormal kidney test result.

Two population-based studies were completed to investigate the second and third findings, as to whether following these guideline-recommended practices was associated with better patient outcomes. These studies included all older adults (>65 years of age) in Ontario, and included patients with and without chronic kidney disease in order to compare the observed associations in both groups.

1.5 Common Methods used across Studies

Studies 1, 3 and 4 were all retrospective cohort studies using administrative data from ICES. In Ontario, most healthcare services are funded through the Ontario Health Insurance Plan program. An exception is outpatient prescription medications which are only covered for a subset of the population, including patients 65 years of age or older. Healthcare databases which collect information on provided services are held at ICES and linked using unique, encoded identifiers.

One of the key data sources used for these studies was laboratory data to identify patients with chronic kidney disease, and to capture patients with acute kidney injury and

hyperkalemia for the outcomes in studies 3 and 4. In the first study, we used linked outpatient laboratory data from one of the three largest community laboratory providers in Ontario, Dynacare, as well as outpatient laboratory data from a network of 12 hospitals in Southwestern Ontario, Cerner. These data sources included approximately 20-30% of all older adults in Ontario. For studies 3 and 4, we used laboratory data from the Ontario Laboratories Information System (OLIS), which was linked to ICES data holdings in 2017. OLIS is an initiative through eHealth Ontario, which includes electronic reporting from all major outpatient laboratories in Ontario and hospitals from 13 of the 14 local health integration networks.[35]

Study 2 was a qualitative descriptive study, which was used to provide an in-depth description of enablers and barriers with minimal interpretation of the data.[36–38] This qualitative component complemented the quantitative studies in this thesis by providing some context to one of the care gaps. Specifically, it addressed why providers may or may not order follow-up laboratory tests to confirm a diagnosis of chronic kidney disease.

1.6 Thesis Content

This thesis is presented in a sandwich thesis format. Following this first chapter, chapter 2 to 5 include manuscripts that are published or submitted to high impact journals for studies 1 to 4, respectively. The manuscript for study 1 (chapter 2), titled "Quality of Care for Patients with Chronic Kidney Disease in the Primary Care Setting: A Retrospective Cohort Study from Ontario, Canada", was published in the *Canadian Journal of Kidney Health and Disease*.[39] This retrospective cohort study measured 11 of

the quality indicators from Tu et al. (2017) to identify the current quality of primary care provided to patients with chronic kidney disease in Ontario.[30]

The manuscript for study 2 (chapter 3), titled "Primary Care Provider Perceptions of Enablers and Barriers to Following Guideline-Recommended Laboratory Tests to Confirm Chronic Kidney Disease: A Qualitative Descriptive Study", was published at *BMC Family Practice*.[40] This qualitative descriptive study included one-on-one semi-structured interviews with primary care providers across Ontario to elucidate the enablers and barriers to completing follow-up laboratory tests to confirm the presence of chronic kidney disease.

The manuscript for study 3 (chapter 4), titled "New Non-Steroidal Anti-Inflammatory Use and the Risk of Acute Kidney Injury and Hyperkalemia in Older Adults: A Population-Based Study", received requested revisions from *Nephrology Dialysis Transplantation*. This study explored the guideline recommendation for avoiding long-term NSAID use among older adults, and specifically among patients with chronic kidney disease. The objective of this study was to assess if prescription NSAID use versus non-use was associated with adverse clinical outcomes. This study also included a prediction model to identify patients most at risk for developing serious complications of acute kidney injury or hyperkalemia after NSAID initiation.

The manuscript for study 4 (chapter 5), titled "Routine laboratory monitoring after starting angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers and the association with clinical outcomes: a cohort study", is under review at *BMJ*. This study explored the guideline-recommended practice of routine serum creatinine and

potassium monitoring after ACEi or ARB initiation among older adults, and specifically among patients with chronic kidney disease. The objective of this study was to see if routine monitoring following ACEi or ARB initiation was associated with a lower risk of all-cause mortality and other adverse outcomes. To address this objective, two studies were completed in two separate North American regions: Kaiser Permanente Northern California, United States and the Institute for Clinical Evaluative Sciences, Ontario, Canada. This method of distributed analytics is useful to determine whether a finding is truly robust and generalizable to other populations.

Finally, chapter 6 includes a summary of the findings, overall implications from the four studies, anticipated future directions, and concluding remarks.

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2. STUDY 1

Nash DM, Brimble S, Markle-Reid M, McArthur E, Tu K, Nesrallah GE, Grill A, Garg AX. Quality of Care for Patients With Chronic Kidney Disease in the Primary Care Setting: A Retrospective Cohort Study From Ontario, Canada. Can J Kidney Health Dis. 2017 May 23; 4:2054358117703059.

Title: Quality of Care for Patients with Chronic Kidney Disease in the Primary Care Setting: a retrospective cohort study from Ontario, Canada

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2.1 ABSTRACT

Background: Patients with chronic kidney disease may not be receiving recommended primary renal care.

Objective: To use recently established primary care quality indicators for chronic kidney disease to determine the proportion of patients receiving recommended renal care.

Design: Retrospective cohort study using administrative data with linked laboratory information.

Setting: Ontario, Canada; 2006 to 2012.

Patients: Patients over 40 years with chronic kidney disease or abnormal kidney function in primary care.

Measurements: Eleven quality indicators for chronic kidney disease identified through a Delphi panel in areas of screening, monitoring, drug prescribing, and laboratory monitoring after initiating an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB).

Methods: We calculated the proportion and cumulative incidence at end of follow-up of patients meeting each indicator and stratified results by age, sex, cohort entry and chronic kidney disease stage.

Results: Less than half of patients received follow-up tests after an initial abnormal kidney function result. Most patients with chronic kidney disease received regular monitoring of serum creatinine (91%), but urine albumin-to-creatinine monitoring was lower (70%). Eighty-four percent of patients did not receive a non-steroidal anti-inflammatory drug prescription of at least two weeks duration. Three quarters of patients

were on an ACE inhibitor or ARB; and 96% did not receive an ACE inhibitor and ARB concurrently. Among patients 50 to 80 years with chronic kidney disease, 65% were on a statin. One quarter of patients who initiated an ACE inhibitor or ARB had their serum creatinine and potassium monitored within 7 to 30 days.

Limitations: This study was limited to people in Ontario with linked laboratory information.

Conclusions: There was generally strong performance across many of the quality of care indicators. Areas where more attention may be needed are laboratory testing to confirm initial abnormal kidney function test results and monitoring serum creatinine and potassium after initiating a new ACE inhibitor or ARB.

Keywords: chronic kidney disease, quality of care, primary care, clinical guidelines, care indicators

What was known before?

Primary care providers are not necessarily targeted by guidelines for chronic kidney disease, and therefore may not be aware of care recommendations for patients with chronic kidney disease. This may have resulted in care gaps for patients with chronic kidney disease in Ontario.

What does this study add?

Ontario patients with chronic kidney disease in the primary care setting are generally receiving appropriate care. Areas for improvement include recognition of chronic kidney disease, and consistent serum creatinine and potassium monitoring after initiating an angiotensin converting enzyme inhibitor or angiotensin receptor blocker.

2.2 BACKGROUND

Currently, 2.9 million Canadians are living with chronic kidney disease.[1] Chronic kidney disease can progress to end-stage kidney disease (approximately 42,000 Canadians in 2013),[2] which has a worse prognosis than most cancers.[3] Early detection and prevention of kidney disease progression is a clinical and research priority in many jurisdictions worldwide, including the province of Ontario, Canada.[4]

Most patients with early stage chronic kidney disease (i.e. stage 1 to 3b) are managed in the primary care setting and are referred to nephrologists if they have advanced disease or are at increased risk of progression. National and international guidelines recommend that patients with abnormal kidney function markers (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2 or urine albumin-to-creatinine ratios [ACR] >3 mg/mmol) receive follow-up tests within three months to establish the diagnosis.[5, 6] Guidelines also recommend that patients with chronic kidney disease should receive ongoing kidney function monitoring, achieve optimal blood pressure control, and reduce cardiovascular risk factors.[5, 6] Primary care providers can meet these care indicators by prescribing statins [7–9] and blood pressure lowering medications including angiotensin converting enzyme (ACE) inhibitors / angiotensin receptor blockers

(ARBs) [10] (but avoiding co-prescription of ACE inhibitors and ARBs),[10–12] performing serum creatinine and potassium tests shortly after initiating an ACE inhibitor or ARB, not prescribing NSAIDs for prolonged periods of time or with high doses,[13, 14] and discussing lifestyle modifications, such as healthy eating, regular physical activity and smoking cessation.[8] Unfortunately, many primary care providers do not always recognize patients with chronic kidney disease,[15, 16] or they are unaware of guidelines for chronic kidney disease care, since primary care providers are not necessarily targeted by guidelines.[15, 17, 18] This means that these recommendations are frequently not followed in routine practice.[19–21]

Care gaps for patients with chronic kidney disease in the primary care setting exist across different international settings (see Additional File 1). Two previous studies have assessed the quality of care for patients with chronic kidney disease in Ontario. One study focused on a group of patients at risk for cardiovascular disease, therefore they only collected information on one quality indicator for a subset of patients with chronic kidney disease in Eastern Ontario.[22] The other study was restricted to primary care physicians involved in an electronic medical record research initiative.[23, 24] These physicians have been involved in related quality of care improvement initiatives, such as diabetes and hypertension care – two known risk factors for chronic kidney disease, so they may be providing higher levels of chronic kidney disease care on average than other Ontario physicians. The purpose of this study was to use recently established quality indicators for chronic kidney disease in the primary care setting to describe the proportion of patients receiving recommended care in Ontario.

2.3 METHODS

Study Design and Research Setting

In Ontario, access to primary healthcare and laboratory tests are covered under the Ontario Health Insurance Plan program; however, outpatient medications are only funded for patients aged 65 years or older, and certain people who are eligible for drug benefit programs.[25] These healthcare encounters are recorded in large administrative healthcare databases, which are linked using unique, encoded identifiers and held at the Institute for Clinical Evaluative Sciences (ICES).

We conducted a retrospective cohort study using the administrative data available at ICES. This study was conducted through the ICES Kidney, Dialysis and Transplantation research program and all analyses were performed at the ICES Western site in London, Ontario. This study was approved by the Sunnybrook Health Sciences Centre Research Ethics Board in Toronto, Ontario. We followed the reporting guidelines for observational studies using the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement (see Additional File 2).[26]

Data Sources

We used linked outpatient laboratory data to identify patients with markers for chronic kidney disease (reduced eGFR and elevated ACR). This data included an electronic network of all 12 hospitals in Southwestern Ontario (Cerner) and all outpatient Dynacare laboratories in Ontario. We used seven other linked databases held at ICES to ascertain information on hospitalizations (Canadian Institute for Health Information's Discharge

Abstract Database [CIHI-DAD]); emergency department visits (CIHI's National Ambulatory Care Reporting System [CIHI-NACRS]); physician billings for healthcare procedures, specialist visits and laboratory tests (Ontario Health Insurance Plan claims database and the ICES Physician database); prescription drug information for individuals over 65 years old (Ontario Drug Benefits database); information on patients with end-stage kidney disease or previous kidney transplants (the Ontario portion of the Canadian Organ Replacement Register [CORR]); and vital status information such as birth and death data (Registered Persons Database).

From 2002 onwards, the 10th edition of the Canadian Modified International Classification of Disease system (ICD-10) was used to record all diagnostic codes in CIHI-DAD and CIHI-NACRS, and the Canadian Classification for Health Interventions (CCI) was used to record all procedural codes.

Patients

In order to assess the performance of the quality of care indicators, we created three cohorts of patients aged 40 years or older accrued between April 1, 2006 and September 30, 2011 based on their kidney function: 1) patients with an initial eGFR value <60 mL/min/1.73 m^2 (eGFR screening cohort), 2) patients with an initial urine ACR concentration >3 mg/mmol (ACR screening cohort), and 3) patients with two eGFR values <60 mL/min/1.73 m^2 separated by at least three months but less than 18 months (chronic kidney disease cohort). Individuals could be in more than one cohort. The eGFR values were calculated based on serum creatinine using the Chronic Kidney Disease

Epidemiology Collaboration formula (CKD-EPI).[27] Since we had no data available on race, all patients were assumed to be non-black in the CKD-EPI equation (a reasonable assumption as less than 5% of the Ontario population is of black race).[28] The date of the laboratory test used to define each cohort was considered the cohort entry date; for the chronic kidney disease cohort this was the date of the second serum creatinine test. We conducted our study from 2006 onwards, since eGFR reporting for laboratories in Ontario began in February 2006.

For the eGFR and ACR screening cohorts, we excluded anyone with evidence of chronic kidney disease in the five years prior to cohort entry (based on codes and nephrology referrals), or any prior evidence of end-stage kidney disease (receipt of either chronic dialysis or a kidney transplant). Similarly, for the chronic kidney disease cohort, we excluded patients with prior evidence of end-stage kidney disease. We did not use urine ACR in combination with eGFR to define our chronic kidney disease cohort, since urine ACR values were not available for most patients.[8]

Development of Quality of Care Benchmarks for Chronic Kidney Disease

A modified Delphi panel funded by the Ontario Renal Network was completed to develop a consensus set of quality primary care indicators for chronic kidney disease.[23] This technique has been used previously to identify quality indicators for cardiac care.[29, 30] The modified Delphi process ensured anonymity and iterative feedback from the group. The panel consisted of stakeholders across Canada including primary care physicians, nephrologists, and nursing and patient representatives. From over 150 initial quality

indicators, the panel considered the evidence and clinical importance of each indicator and agreed on 17 final quality indicators. Based on the data available in our data sources, we were able to measure 10 of these quality indicators for the current study, with the addition of one other indicator. See Table 1 for the definitions of the 11 quality indicators used in this study.

Definitions of Quality Indicators

Patients were followed forward in the datasets from 30 days to 18 months after their index date depending on the quality indicator. The first three quality indicators looked at screening or recognition of chronic kidney disease among the eGFR and ACR screening cohorts. Indicators four and five looked at monitoring of kidney function with serum creatinine and urine albumin-to-creatinine measures at least once in the 18 months following evidence of chronic kidney disease. The screening and monitoring indicators used physician billing codes to ascertain receipt of laboratory tests. Indicators six to nine assessed appropriate use of medications among patients with chronic kidney disease in the one year following evidence of chronic kidney disease (prescribing ACE inhibitors or ARBs for patients with diabetes and/ or ACR > 3 mg/ mmol, avoiding co-prescription of ACE inhibitors and ARBs, prescribing statins, and avoiding prolonged use of prescription NSAIDs). The last two quality indicators looked at monitoring serum creatinine and serum potassium levels (based on physician billing codes) in the seven to 30 days after patients were initiated on an ACE inhibitor or ARB. For the medication indicators we excluded patients less than 66 years of age, which allowed for one full year of baseline

medications for review (as previously mentioned, outpatient drug coverage is a universal benefit for persons 65 years and older living in Ontario). We were not able to capture over-the-counter NSAID use. See Additional Files 3a and 3b for administrative codes and drug names used to define indicators.

Statistical Analyses

All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC). We calculated the percentage of patients meeting each indicator based on the definitions for each numerator and denominator. Prior to calculating these percentages, we excluded patients who died during the follow-up period to ascertain each indicator. As a secondary analysis, we calculated the cumulative incidence function censored for death of each indicator at end of follow-up estimated using the exponential equation [$1\text{-}e^{(-IR*T)}$; where e is a mathematical constant, IR = incidence rate or number of people with an event over person-time at risk, and T = time period of interest].

We stratified the percentage of patients meeting each indicator by age (40 to <65, 65 to <80 and 80 years or older), sex, cohort entry period (April 2006 to December 2008 and January 2009 to September 2011), and baseline eGFR levels (60 mL/min/1.73 m^2 or greater, 44 to 59 mL/min/1.73 m^2 and < 44 mL/min/1.73 m^2]). Note that indicator 3, assessing repeat ACR values, was the only indicator that included patients with eGFR ≥ 60 mL/min/1.73 m^2; based on the cohort definitions, only patients with eGFR < 60 mL/min/1.73 m^2 were included in the assessment of the other indicators. We focused on variation across these variables because age and gender disparities in quality of care have

been described previously for chronic kidney disease and other related conditions.[31–35] We were also interested to see if there were changes over time. Finally, quality of care indicators for chronic kidney disease have been shown to vary based on chronic kidney disease stage.[36–41]

Baseline Characteristics

We examined the baseline characteristics of the three different cohorts. These characteristics included demographics (age, sex, rural or urban residence, and income quintile), baseline kidney function (serum creatinine, eGFR and urine ACR), healthcare use in the past year (number of hospitalizations, emergency room visits, primary care visits, general internist visits and nephrology visits), Johns Hopkins Adjusted Clinical Groups to estimate intensity of healthcare resource use in the past year,[42] comorbidities based on Johns Hopkins Expanded Diagnostic Clusters in the past year (ischemic heart disease, congestive heart failure, cardiac arrhythmia, acute myocardial infarction, cardiac arrest, hypertension, diabetes, chronic liver disease, malignant neoplasms, cerebrovascular disease, and peripheral vascular disease), and prescription drugs filled in the previous 120 days by patients over the age of 65 years (ACE inhibitors, ARBs, statins, and diabetes medications).

We summarized binary and categorical characteristics by proportions and continuous characteristics by means, standard deviations, medians and interquartile ranges (IQR; i.e. 25^{th} and 75^{th} percentiles).

2.4 RESULTS

Patients

See Figure 1 for the flow diagram of patients included in the three cohorts. There were 223,994 patients in the eGFR screening cohort, 132,442 patients in the ACR screening cohort and 184,557 patients in the chronic kidney disease cohort. The total number of unique patients included in the study was 410,409. There were 28,442 patients in both the eGFR screening and ACR screening cohorts, 25,935 patients in both the ACR screening and chronic kidney disease cohorts, 92,688 patients in both the eGFR screening and chronic kidney disease cohorts, and 16,521 patients included in all three cohorts.

Baseline Characteristics

See Table 2 for the baseline characteristics of the three cohorts. The median (interquartile range) age of patients in the ACR screening cohort was 64 (IQR 54 to 74), whereas the median (IQR) age in the eGFR screening and chronic kidney disease cohorts was 74 (IQR 66 to 81) and 77 (IQR 70 to 83), respectively. Half of the patients in the ACR screening cohort were female compared to approximately 60% of the patients in the eGFR screening and chronic kidney disease cohorts. Among patients in the ACR cohort with available serum creatinine tests (89%) in the previous year, approximately 80% had eGFR $\geq$60 mL/min/1.73 m^2. Only 19% and 31% of the screening and chronic kidney disease cohorts, respectively, had urine ACR values available in the previous year. Among these patients, 68% in the screening cohort and 58% in the chronic kidney disease

cohort had a urine ACR value <3 mg/mmol. Approximately 54% of patients in the ACR screening cohort, 23% of patients in the eGFR screening cohort and 31% of patients in the chronic kidney disease cohort had diabetes.

Quality Indicator Performance

See Table 3 for the number, proportion and cumulative incidence of patients meeting each of the quality indicators. Median follow-up times ranged from 158 to 395 days depending on the indicator (see Additional File 4). Proportions and cumulative incidence at follow-up for each indicator were similar for most indicators. Overall, screening or recognition of chronic kidney disease was around 50% (ranged from 42% for repeat urine ACR testing following an initial ACR >3 mg/mmol to 55% for urine ACR testing done on the same day (36%) or in the following six months after an initial eGFR value <60 mL/min/1.73 m^2). The 6-month cumulative incidence for this latter indicator was 65%. Regular monitoring of kidney function was high for serum creatinine tests (91%) but was lower for urine albumin-to-creatinine tests (70%). Most (84%) patients with chronic kidney disease and 66 years or older were not receiving an NSAID prescription for two weeks or more in the one year following their chronic kidney disease date. The majority of patients 66 years or older with chronic kidney disease who also had diabetes and/ or proteinuria were receiving an ACE inhibitor or ARB (75%) in the one year following their chronic kidney disease date, and 96% were not receiving an ACE inhibitor and an ARB concurrently. Among patients between ages 66 and 80 years, 65% received a statin. Monitoring of serum creatinine and serum potassium in the 7 to 30 days after initiating an

ACE inhibitor or ARB for patients aged 66 years or older with chronic kidney disease was around 25%.

The percentage of patients meeting each quality indicator when stratified by age, sex, cohort entry period and baseline eGFR are shown in Additional Files 5a-d. Among most quality indicators, proportions were higher for males compared to females, with the exception of the indicators for repeat urine albumin-to-creatinine test following an abnormal ACR result (44% for females and 40% for males). The screening indicators generally showed a decreasing trend with age and an increasing trend with severity of chronic kidney disease, except for the repeat urine albumin-to-creatinine screening indicator. Serum creatinine monitoring among patients with chronic kidney disease was similar when stratified by all four variables, where urine albumin-to-creatinine monitoring decreased with age (>80 *vs* 65 to <80 years) from 75% to 64%. Among the prescription indicators for patients aged 66 and older, not prescribing ACE inhibitors and ARBs concurrently increased over time (95% to 98%) and the frequency of prolonged use of prescription NSAIDs did not change over time. Prescriptions for ACE inhibitors or ARBs increased over time (74% to 78%) and decreased with age (77% to 72%). Prescriptions for statins increased with severity of chronic kidney disease (64% to 68%) and decreased with age (65% to 62%). Finally, for the monitoring of ACE inhibitor and ARB indicators, monitoring was higher for patients with eGFR < 44 mL/min/1.73 m^2 compared to patients with eGFR 44 to 59 mL/min/1.73 m^2 (32% *vs* 22% for serum creatinine and 30% *vs* 21% for serum potassium).

2.5 DISCUSSION

This is the largest and most comprehensive population-based study to assess the quality of renal care among patients being screened for, or who have, chronic kidney disease in the primary care setting in Ontario, Canada.

Overall, we found that most quality of care indicators were met by primary care providers. For instance, it was reassuring that the majority of patients with chronic kidney disease and proteinuria/ diabetes were receiving ACE inhibitors or ARBs, and that patients were not being prescribed NSAIDs for prolonged use or simultaneously receiving ACE inhibitors and ARBs.

We found that around half of the patients with an initial abnormal eGFR or ACR did not receive follow-up tests to confirm whether chronic kidney disease was present or not. This is consistent with previous literature on chronic kidney disease recognition. Another Ontario cohort study, which included physicians enrolled in an electronic medical record research initiative, found that 48% and16% of patients with initial abnormal eGFR received repeat serum creatinine and follow-up albumin-to-creatinine testing, respectively.[23] Similarly, a large retrospective cohort study in the United Kingdom showed that only 25% of patients with incident chronic kidney disease based on laboratory values were registered as having chronic kidney disease, and only 36% of patients had an ACR test completed over the study period.[40] This lack of confirmatory tests may be partially explained by primary care physicians' concerns for over-diagnosis. For example, a survey of primary care providers in the United States found that 30% of physicians would not classify patients as having chronic kidney disease if their eGFR was

between 45 and 59 L/min/1.73m^2 and 55% would not diagnose patients with chronic kidney disease if they had an eGFR >60 L/min/1.73m^2 with microalbuminuria.[18] An alternative explanation could be that patients are not receiving follow-up confirmatory tests against the advice of their primary care providers. Furthermore, primary care physicians may view low eGFR as part of the normal aging process rather than as a disease.[43] Our results showed a decreasing trend of screening with age. Primary care physicians may be less likely to screen older individuals with reduced life expectancies, since they are not likely to benefit from chronic kidney disease care management.

After the presence of chronic kidney disease is established in our study (i.e. two eGFR values <60 mL/min/1.73 m^2 between three to 18 months apart), patients are found to be receiving adequate monitoring of kidney function in the following 18 months; however, this is higher for serum creatinine (91%) compared to urine albumin-to-creatinine (70%) monitoring. The lower adherence to urine albumin-to-creatinine monitoring is consistent with another Ontario cohort study, which found that only 52% of patients with chronic kidney disease received a urine albumin-to-creatinine test over a 12-month period among 84 primary care practices in Eastern Ontario.[22] A province-wide report in Alberta also showed lower adherence to albumin-to-creatinine test monitoring of 32% in the previous two years.[44] Furthermore, a cohort study in the United States found an even larger discrepancy between annual monitoring for serum creatinine and urine albumin-to-creatinine among patients with chronic kidney disease: 86% and 30%, respectively.[45] Primary care physicians are generally in agreement about the importance of regular serum creatinine testing for patients with chronic kidney disease,

but they are less in agreement about the importance of regular urine albumin-to-creatinine testing for chronic kidney disease in the absence of diabetes.[18, 34] For instance, the American College of Physicians released guidelines in 2013, recommended against urine albumin-to-creatinine monitoring among patients who are taking an ACE inhibitor or ARB; however, this was a weak recommendation based on low-quality evidence.[46] Some reported barriers include assumptions that the urine albumin-to-creatinine test does not impact patient management, concerns that there are more pressing issues for patient care or not enough time, and the belief that urine albumin-to-creatinine monitoring is not recommended for patients with chronic kidney disease in the absence of diabetes.[18]

In regards to appropriate prescribing indicators, we found that the majority of patients aged 66 years and older with chronic kidney disease, diabetes and/ or ACR > 3 mg/mmol are receiving an ACE inhibitor or an ARB (74%). It is unlikely that much improvement can be made for this indicator, since some of the patients have contra-indications including a history of prior adverse events with these drugs. Another Ontario cohort study also found that 75% of patients with diabetes and albuminuria were on an ACE inhibitor or ARB.[23] A province-wide report on chronic kidney disease care in Manitoba also reported high rates of ACE inhibitor and ARB use (up to 80%), especially among patients with diabetes and at high-risk of chronic kidney disease progression.[47]

It is reassuring that only a small proportion of patients aged 66 years and older were receiving ACE inhibitors and ARBs concurrently and that this decreased slightly over time. This decrease over time from 2006-2008 to 2009-2011 coincides with the timing of the press release from the Heart and Stroke Foundation in 2009.[12] This press

release warned against co-prescribing of ACE inhibitors and ARBs, which was based on evidence from a large international clinical trial.[11] We used a conservative definition to capture ACE inhibitor and ARB co-prescribing in order to avoid misclassifying patients who switched from one drug to the other, so we may have missed some cases. However, our results are consistent with two previous studies: a large cohort study in the United Kingdom and a Dutch study focusing on patients with diabetes and chronic kidney disease, which found that 98% and 96% of patients, respectively, were not taking an ACE inhibitor and ARB concurrently.[41, 48]

Many patients in our study aged 66 to 80 years with non-dialysis dependent chronic kidney disease received a statin (65%); although there is room for improvement. A province-wide study in Alberta found similar results among patients with chronic kidney disease and diabetes.[44] Our results are higher than the statin prescribing proportions observed by previous studies in the United States (ranging from 16% to 57%).[39, 45, 49–51] Our results are more consistent with studies in Australia and Asia (ranging from 59% to 87%) and a study in the Netherlands (74%).[36, 48, 52, 53] We only looked at statin prescribing up until 2012; guidelines recommending statin use for patients with chronic kidney disease were released in 2013,[54] so there may be improvement in more recent years.

Only 16% of patients aged 66 and older with chronic kidney disease in our study were receiving an NSAID prescription for longer than two weeks. However, we could not capture use of non-prescription NSAIDs. Prolonged cumulative NSAID use or high dose of NSAIDs (versus low dose) among patients with reduced kidney function has been

shown to be associated with accelerated kidney function decline.[13, 14] Our findings align with previous studies from Canada, the United States, the United Kingdom and Australia where NSAID prescribing among patients with chronic kidney disease ranged from 1% to 16%.[23, 37, 38, 45, 55, 56] In a qualitative study of primary care physicians' attitudes and knowledge about chronic kidney disease, it was described that physicians are aware that NSAIDs should be avoided in patients with chronic kidney disease but they generally prescribe NSAIDs to patients with chronic kidney disease who they deem to be at low risk of complications.[17]

Our results showed that there is poor laboratory monitoring among patients aged 66 and older with chronic kidney disease who were initially prescribed an ACE inhibitor or an ARB – over three quarters of patients did not have their serum creatinine and potassium monitored in the month following their initial prescription. This may be concerning since ACE inhibitor and ARB use in patients with chronic kidney disease is associated with increased short-term elevation of serum creatinine and potassium.[57, 58] With adequate monitoring of patients' serum creatinine and potassium levels, the long-term benefits of these prescriptions outweigh these short-term risks.[57] Our results are consistent with a Dutch study that also found only 34% and 28% of patients (not all with chronic kidney disease) received serum creatinine and serum potassium monitoring, respectively, within three weeks of initiating an ACE inhibitor or ARB.[59] Another study reported about 50% serum creatinine and potassium monitoring after initiating an ACE inhibitor among patients with hypertension, but they allowed a six month follow-up period in which tests could be performed.[60]

Strengths and Limitations

This is the largest population-based study conducted on the quality of primary care for patients with chronic kidney disease. In addition to calculating the percentage of people meeting each indicator, we also provided the cumulative incidence at the end of follow-up, censoring for death. This provides a more accurate estimate by allowing patients who died during the follow-up period to still be eligible to meet each indicator in the period prior to their death date. However, given the small number of patients who died during follow-up for each indicator, the cumulative incidence estimates are very similar to the percentages.

Our study has some limitations. The laboratory data used to define our cohorts was from one of Ontario's three largest commercial laboratories and has wide coverage across Ontario, but likely only includes approximately 20% of Ontario's chronic kidney disease population. As such, our results may not be representative of all patients at risk for, or with, chronic kidney disease in Ontario. However, physician billing codes were used to ascertain outpatient tests completed at all Ontario commercial laboratories for the screening, monitoring and ACE inhibitor/ ARB follow-up test indicators. As such, this does not affect the internal validity of our indicator calculations. The Ontario Laboratory Information System data is an electronic database capturing all outpatient laboratories in Ontario. This data is in the process of being linked to the ICES data holdings, so in future studies we will be able to provide more generalizable Ontario-wide reports on quality indicators for chronic kidney disease.

Our study was also limited by other healthcare data available in our data sources. Through the modified Delphi panel process, 17 quality of care indicators were identified but only 11 indicators could be assessed using healthcare administrative data. For example, we did not have information on blood pressure to determine whether targets were being met. Our drug indicators were also limited to patients 65 years or older, so we cannot make any observations on appropriate prescribing for patients with chronic kidney disease under 65 years. Furthermore, NSAIDs are also available over-the-counter, but we could only capture prescription NSAIDs with our data sources.

It is also important to note that our study did not capture people with chronic kidney disease who went untested (unidentified) in routine care. As such, our screening indicators only apply to patients who have received at least one abnormal test in our data sources during the study period. We did not assess screening in patients with risk factors for chronic kidney disease (e.g., cardiovascular disease, diabetes or hypertension).

CONCLUSIONS

Overall, we found high proportions of patients meeting most of the quality of care indicators including regular chronic kidney disease monitoring and ACE inhibitor/ ARB use; however, improvement is still needed for other care indicators such as screening and recognition of chronic kidney disease, and follow-up monitoring of serum potassium and serum creatinine for new ACE inhibitor or ARB users. Future population-based studies are needed to confirm these findings, as well as studies to determine the potential impact on patient outcomes of not meeting these indicators. Future qualitative studies exploring

the barriers and facilitators to implementation of the chronic kidney disease guidelines in Ontario primary care are warranted.

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List of Abbreviations used:

ACE, Angiotensin Converting Enzyme

ACR, Albumin-to-Creatinine Ratio

ADG, Aggregated Diagnosis Groups

ARB, Angiotensin Receptor Blocker

CCI, Canadian Classification for Health Interventions

CIHI, Canadian Institute for Health Information

CKD, Chronic Kidney Disease

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration formula

DAD, Discharge Abstract Database

eGFR, estimated Glomerular Filtration Rate

FH, Framingham Heart Study

f/u, follow-up

K, Potassium

KP, Kaiser Permante

ICD-10, 10th edition of the Canadian Modified International Classification of Disease system

ICES, Institute for Clinical Evaluative Sciences

IQR, Interquartile Range

KDIGO, Kidney Disease Improving Global Outcomes

NACRS, National Ambulatory Care Reporting System

NHANES, National Health and Nutrition Examination Survey

NSAIDs, Non-steroidal Anti-inflammatory Drugs

SCr, Serum Creatinine

SD, Standard Deviation

UK, United Kingdom

US, United States

VA, Veterans Affairs

2.7 DECLARATIONS

Ethics approval and consent to participate: This study was approved by the Sunnybrook Health Sciences Centre Research Ethics Board in Toronto, Ontario. Participant consent for this study was waived.

Consent for publication: Not applicable.

Availability of data and materials: We cannot share the data used for this project due to privacy requirements at ICES. Only aggregated data as presented in this manuscript can be shared.

Competing risks: AXG was supported by the Dr. Adam Linton Chair in Kidney Health Analytics. AXG, SB, GEN and AG are Provincial Medical Leads for the Ontario Renal Network. All other authors declare that they have no competing interests.

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Authors' contributions: DMN and AXG developed the initial study plan. KT developed the initial literature review for chronic kidney disease care indicators and led the Delphi Panel. SB, MMR and EM provided input and approved of the study and analysis plan. DN completed all analyses with the assistance of EM. All authors interpreted the results. DN drafted the initial manuscript and all other authors critically reviewed and revised the manuscript. All authors read and approved the final manuscript.

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2.8 TABLES & FIGURES

Figure 1. Flow Diagrams of Participant Selection

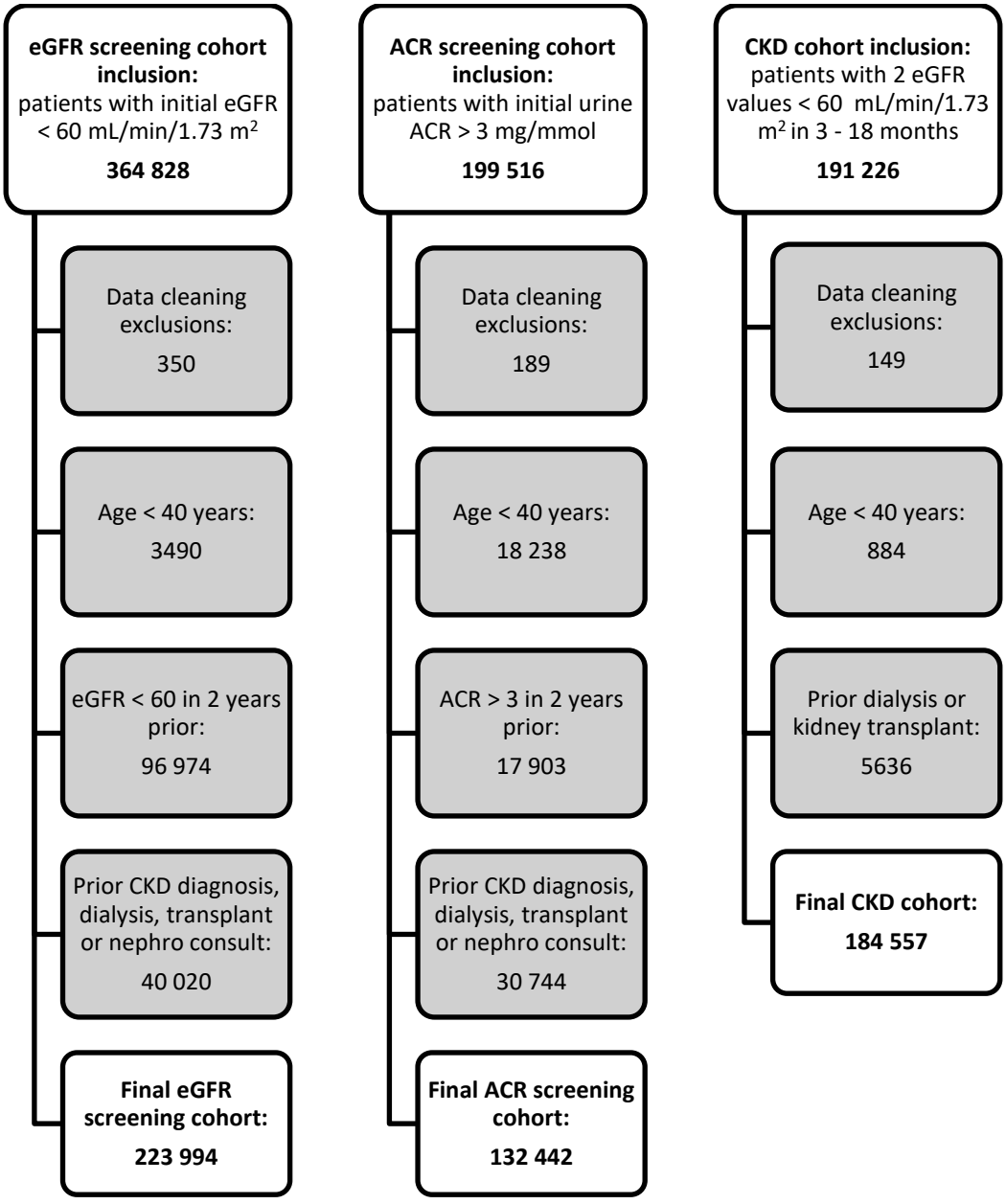

Table 1. Definitions of Quality of Care Indicators for Chronic Kidney Disease

#	Numerator	Denominator
Screening/ Recognition of CKD		
1	Patients who receive a repeat outpatient serum creatinine test in the following six months, based on laboratory data or billing codes.	Patients with an initial eGFR <60 mL/ min/ 1.73 m^2 (eGFR screening cohort).
2	Patients who receive an outpatient urine albumin-to-creatinine test on the same day as the initial serum creatinine tests or in the following six months, based on laboratory data for random urine ACR or billing codes.	
3	Patients who receive a repeat outpatient urine albumin-to-creatinine test in the following six months.	Patients with an initial ACR>3 mg/ mmol (ACR screening cohort).
Monitoring of Kidney Function		
4	Patients with an outpatient serum creatinine test in the following 18 months.	Patients with two eGFR values <60 mL/ min/ 1.73 m^2 separated by at least three months but less than 18 months (chronic kidney disease cohort).
5	Patients with an outpatient urine albumin-to-creatinine in the following 18 months.	
Use of Appropriate Medication		
6	Patients who are not prescribed an NSAID for longer than two weeks at any time in the one year following the date of the second eGFR value.	Patients aged 66 and older with two eGFR values <60 mL/ min/ 1.73 m^2 separated by at least three months but less than 18 months (chronic kidney disease cohort).
7	Patients who are not simultaneously receiving both an ACE inhibitor and an ARB at any time in the one year following the date of the second eGFR value. This was defined as a prescription for an ARB filled during the continuous use of an ACE inhibitor or an ACE inhibitor filled during the continuous use of an ARB.	
8	Patients who are prescribed an ACE inhibitor or ARB at any time in the one year following the date of the second eGFR value.	Patients aged 66 and older with two eGFR values <60 mL/ min/ 1.73 m^2 separated by at least three months but less than 18 months who also have evidence of ACR ≥3 mg/ mmol and/ or diabetes.
9	Patients who are prescribed a statin at any time in the one year following the date of the second eGFR value.	Patients aged 66 and older with two eGFR values <60 mL/min/1.73 m^2 separated by at least three months but less than 18 months who are between the ages of 66 and 80 years.
Monitoring of ACE inhibitors and ARBs		
10	Patients who receive an outpatient serum creatinine test 7-30 days after initial prescription date.[1]	Patients aged 66 and older with two eGFR values <60 mL/ min/ 1.73 m^2 separated by at least three months but less than 18 months who receive an initial prescription for an ACE inhibitor or ARB.
11	Patients who receive an outpatient serum potassium test 7-30 days after initial prescription date.	

[1]This indicator was originally identified from the Delphi panel but was not included in the final list of indicators because initial prescription could not be measured using electronic medical record data.

Abbreviations: ACE, Angiotensin Converting Enzyme; ACR, Albumin-to-Creatinine Ratio; ARB, Angiotensin Receptor Blockers; CKD, Chronic Kidney Disease; eGFR, estimated Glomerular Filtration Rate; NSAIDs, Non-Steroidal Anti-Inflammatory Drugs.

Table 2. Baseline Characteristics for the Three Study Cohorts

Characteristic	eGFR Screening Cohort	ACR Screening Cohort	CKD Cohort
N total	223,994	132,442	184,557
Demographics and Baseline Kidney Function			
Cohort entry period			
2006 – 2008	129,643 (57.9%)	60,552 (45.7%)	117,002 (63.4%)
2009 – 2011	94,351 (42.1%)	71,890 (54.3%)	67,555 (36.6%)
Age at cohort entry, years			
Mean (SD)	73.0 (11.0)	64.4 (12.7)	75.7 (10.3)
Median (IQR)	74.0 (66.0-81.0)	64.0 (54.0-74.0)	77.0 (70.0-83.0)
40-64	49,439 (22.1%)	67209 (50.7%)	26,368 (14.3%)
65-79	106,392 (47.5%)	47033 (35.5%)	85,530 (46.3%)
≥ 80	68,163 (30.4%)	18200 (13.7%)	72,659 (39.4%)
Female	132,631 (59.2%)	65923 (49.8%)	106,563 (57.7%)
Rural location	29,950 (13.4%)	11645 (8.8%)	23,237 (12.6%)
Income based socioeconomic status			
Quintile 1 (low)	44,482 (19.9%)	29,601 (22.4%)	37,778 (20.5%)
Quintile 2	48,039 (21.4%)	30,336 (22.9%)	40,933 (22.2%)
Quintile 3 (medium)	45,076 (20.1%)	26,869 (20.3%)	37,209 (20.2%)
Quintile 4	43,191 (19.3%)	24,402 (18.4%)	34,884 (18.9%)
Quintile 5 (high)	42,528 (19.0%)	20,853 (15.7%)	33,150 (18.0%)
Missing	678 (0.3%)	381 (0.3%)	603 (0.3%)
SCr at cohort entry or in the past year			
Patients with SCr values	223,994 (100.0%)	117,873 (89.0%)	184,557 (100.0%)
Mean (SD)	107 (33)	81 (29)	119 (42)
Median (IQR)	103 (90-116)	76 (65-92)	110 (94-129)
eGFR values (mL/min/1.73m²) at cohort entry or in the past year			
Patients with eGFR value	223,994 (100.0%)	117,873 (89.00%)	184,557 (100.0%)
Mean (SD)	52 (8)	80 (21)	47 (11)
Median (IQR)	55 (49-58)	83 (65-96)	50 (41-55)
≥60	0 (0.0%)	95,585 (81.1%)	0 (0.0%)
45-59	187,682 (83.8%)	14,597 (12.4%)	120,181 (65.1%)
30-44	30,536 (13.6%)	6,279 (5.3%)	48,299 (26.2%)
15-29	5,156 (2.3%)	1,299 (1.1%)	14,595 (7.9%)
<15	620 (0.3%)	113 (0.1%)	1,482 (0.8%)
ACR values (mg/mmol) at cohort entry or in the past year			
Patients with ACR value	42,839 (19.1%)	132,442 (100.0%)	57,723 (31.3%)
< 3	28,957 (67.6%)	0 (0.0%)	33,626 (58.3%)

Characteristic	eGFR Screening Cohort	ACR Screening Cohort	CKD Cohort
3-30	10,721 (25.0%)	118,365 (89.4%)	16,779 (29.1%)
>30	3,161 (7.4%)	14,077 (10.6%)	7,318 (12.7%)
Health care use in previous one year			
Number of previous hospitalizations			
0	190,344 (85.0%)	119,364 (90.1%)	147,635 (80.0%)
1-2	30,551 (13.6%)	12,142 (9.2%)	32,506 (17.6%)
3-4	2706 (1.2%)	830 (0.6%)	3748 (2.0%)
>4	393 (0.2%)	106 (0.1%)	668 (0.4%)
Number of previous emergency room visits			
0	150,375 (67.1%)	97,101 (73.3%)	115,745 (62.7%)
1-2	57,982 (25.9%)	28,790 (21.7%)	51,966 (28.2%)
3-4	10,920 (4.9%)	4579 (3.5%)	11,407 (6.2%)
>4	4717 (2.1%)	1972 (1.5%)	5439 (2.9%)
Number of previous primary care visits			
0	4334 (1.9%)	2572 (1.9%)	3058 (1.7%)
1-3	41,042 (18.3%)	27,063 (20.4%)	18,602 (10.1%)
4-6	54,296 (24.2%)	33,422 (25.2%)	38,554 (20.9%)
7-9	42,372 (18.9%)	25,721 (19.4%)	35,486 (19.2%)
>9	81,950 (36.6%)	43,664 (33.0%)	88,857 (48.1%)
Number of previous internist visits			
0	159,734 (71.3%)	100,810 (76.1%)	123,250 (66.8%)
1-2	43,777 (19.5%)	22,462 (17.0%)	37,008 (20.1%)
3-4	9448 (4.2%)	4825 (3.6%)	10,462 (5.7%)
>4	11,035 (4.9%)	4345 (3.3%)	13,837 (7.5%)
Number of previous nephrologist visits			
0	215,832 (96.4%)	126,880 (95.8%)	152,208 (82.5%)
1	6829 (3.0%)	4799 (3.6%)	14,048 (7.6%)
≥2	1333 (0.6%)	763 (0.6%)	18,301 (9.9%)
Comorbidities – defined by ADG in 1 year prior			
Overall ADG score			
Mean	5.6 (3.2)	5.0 (3.0)	6.3 (3.3)
Median	5.0 (3.0 – 8.0)	5.0 (3.0 – 7.0)	6.0 (4.0 – 8.0)
0-4	93,120 (41.6%)	66,151 (49.9%)	62,164 (33.7%)
5-9	103,828 (46.4%)	54,991 (41.5%)	91,371 (49.5%)
10-14	25,012 (11.2%)	10,546 (8.0%)	28,086 (15.2%)
15-19	2,000 (0.9%)	747 (0.6%)	2,893 (1.6%)
≥20	34 (0.0%)	7 (0.0%)	43 (0.0%)
Ischemic heart disease	39,074 (17.4%)	16,563 (12.5%)	42,321 (22.9%)

Characteristic	eGFR Screening Cohort	ACR Screening Cohort	CKD Cohort
Congestive heart failure	16,147 (7.2%)	5,265 (4.0%)	21,643 (11.7%)
Cardiac arrhythmia	24,071 (10.7%)	9,014 (6.8%)	26,786 (14.5%)
Acute myocardial infarction	4,961 (2.2%)	1,782 (1.3%)	5,518 (3.0%)
Cardiac arrest, shock	363 (0.2%)	130 (0.1%)	419 (0.2%)
Hypertension	111,387 (49.7%)	59,471 (44.9%)	103,102 (55.9%)
Diabetes	51,681 (23.0%)	70,947 (53.6%)	57,833 (31.3%)
Chronic liver disease	1,604 (0.7%)	659 (0.5%)	1,331 (0.7%)
Malignant neoplasms	11,899 (5.3%)	3953 (2.9%)	10,647 (5.8%)
Cerebrovascular disease	11,431 (5.1%)	4,051 (3.1%)	12,311 (6.7%)
Peripheral vascular disease	4,870 (2.2%)	2,284 (1.7%)	5,541 (3.0%)
Baseline medications in 120 days prior			
Number of patients >65 years with available drug data	174,555 (77.9%)	65,233 (49.3%)	158,189 (85.7%)
ACE inhibitors	70,228 (40.2%)	30,365 (46.5%)	74,200 (46.9%)
ARBs	42,535 (24.4%)	18,994 (29.1%)	46,595 (29.5%)
Statins	82,128 (47.0%)	40,046 (61.4%)	88,110 (55.7%)
Diabetes drugs[1]	34,487 (19.8%)	31,723 (48.6%)	41,708 (26.4%)

Abbreviations: ACE, Angiotensin Converting Enzyme; ACR, Albumin-to-Creatinine Ratio; ADG, Aggregated Diagnosis Groups; ARB, Angiotensin Receptor Blockers; CKD, Chronic Kidney Disease; eGFR, estimated Glomerular Filtration Rate; IQR, Interquartile Range; SCr, serum creatinine; SD, Standard Deviation

[1]Diabetes drugs included insulin and oral anti-glycemic medications.

Table 3. Number and Proportion of Patients Meeting Quality of Care Indicators

	Indicator	Total	Events	%	CIF[1] (%)
Screening/ Recognition of CKD					
1	% of patients with an initial eGFR <60 mL/min/1.73 m^2 who received a repeat serum creatinine test in the following six months.	218,309	107,483	49	50
2	% of patients with an initial eGFR <60 mL/min/1.73 m^2 who received a urine albumin-to-creatinine test in the following six months (including the day of the initial eGFR).	218,309	120,876	55	65
3	% of patients with an initial ACR >3 mg/mmol who received a repeat urine albumin-to-creatinine test in the following six months.	131,178	55,583	42	42
Monitoring of Kidney Function					
4	% of patients with CKD (based on two eGFR values < 60 mL/min/1.73 m^2) who received a serum creatinine test in the following 18 months.	168,016	152,828	91	91
5	% of patients with CKD who received a urine albumin-to-creatinine test in the following 18 months.	168,016	117,852	70	70
Use of Appropriate Medication					
6	% of patients aged 66 and older with CKD who were not prescribed an NSAID for longer than two weeks.	147,921	23,609	84	84
7	% of patients aged 66 and older with CKD who are not simultaneously receiving both an ACE inhibitor and an ARB.	147,921	5551	96	97
8	% of patients aged 66 and older with CKD with ACR ≥3 mg/mmol and/ or diabetes who are prescribed an ACE inhibitor or ARB.	67,285	50,499	75	74
9	% of patients 66 to 80 years of age with CKD who received a statin.	89,543	58,314	65	65
Monitoring of ACE inhibitors and ARBs					
11	% of patients aged 66 and older with CKD who received a serum creatinine test 7-30 days after initial ACE inhibitor/ ARB prescription.	10,794	2,783	26	27
10	% of patients aged 66 and older with CKD who received a serum potassium test 7-30 days after initial ACE inhibitor/ ARB prescription.	10,794	2,590	24	25

[1]Cumulative incidence is reported at the end of follow-up for each indicator.

Abbreviations: ACE, Angiotensin Converting Enzyme; ACR, Albumin-to-Creatinine Ratio; ARB, Angiotensin Receptor Blockers; CKD, Chronic Kidney Disease; CIF, cumulative incidence function; eGFR, estimated Glomerular Filtration Rate; NSAIDs, Non-Steroidal Anti-Inflammatory Drug.

2.9 APPENDICES

Appendix 1: Literature Review of Quality of Care for Patients with Chronic Kidney Disease in the Primary Care Setting across Different Geographic Regions

Appendix 2: Checklist of Recommendations for Reporting of Observational Studies using the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement

Appendix 3:

- Appendix 3a: Administrative Codes used to Define Chronic Kidney Disease Quality of Care Indicators
- Appendix 3b: Drugs used to Define Chronic Kidney Disease Quality of Care Indicators

Appendix 4: Distribution of Follow-up Times to Assess Each Indicator (Reported in Years)

Appendix 5:

- Appendix 5a: Screening Indicators Stratified by Age, Sex, Cohort Entry Period and Estimated Glomerular Filtration Rate
- Appendix 5b: Kidney Function Monitoring Indicators Stratified by Age, Sex, Cohort Entry Period and Estimated Glomerular Filtration Rate
- Appendix 5c: Prescribing Indicators Stratified by Age, Sex, Cohort Entry Period and Estimated Glomerular Filtration Rate
- Appendix 5d: Monitoring of ACE Inhibitor or ARB Indicators Stratified by Age, Sex, Cohort Entry Period and Estimated Glomerular Filtration Rate

Appendix 1: Literature Review of Quality of Care for Patients with Chronic Kidney Disease in the Primary Care Setting across Different Geographic Regions

Population & Setting	Quality of Care Indicators (see Table 1 for definitions)										
	1	2	3	4	5	6	7	8	9	10	11
	Repeat eGFR	f/u ACR	Repeat ACR	SCr monitor	ACR monitor	No NSAID	No ACEi & ARB	ACEi/ ARB	Statin	ACEi/ ARB f/u SCr or K	
Ontario, 2016; 139,535 patients total; 6950 with CKD [1]	48%	16%			34%	99%	99%	75%	60%		
Alberta, 2012-2013; 96,480 patients with CKD [2]					83% in past 24 months			65 – 85%[1]	40 – 65%[1]		
Manitoba, 2012; 71,758 patients with CKD [3]								21 - 81%[2]			
Eastern Ontario, 2008-2010; 4931 patients total; 923 with CKD [4]					52% in past 12 months						
US, 2011-2012; 9307 patients with diabetes; 2396 also with stage 3-5 CKD [5]	22%[3]			85% in 15 months	69% in 15 months[4]						
US (NHANES), 2001-2010; 9915 patients; 1428 with CKD (excluding stage 5) [6]									30%[5]		
US, 2004-2008; 11,774 patients with stage 3-4 CKD [7]				86% (annual)	30% (annual)	90%			42%	75%	

Population & Setting	Quality of Care Indicators (see Table 1 for definitions)										
	1	2	3	4	5	6	7	8	9	10	11
	Repeat eGFR	f/u ACR	Repeat ACR	SCr monitor	ACR monitor	No NSAID	No ACEi & ARB	ACEi/ ARB	Statin	ACEi/ ARB f/u SCr or K	
US, 2005; 70,154 patients with stage 3-5 pre-dialysis CKD from the VA [8]						85%					
US, 2002-2005; 519 patients with stage 3 CKD [9]					9%			30 - 53%[1]			
US (KP), 2002-2005; 3157 patients with 2 eGFRs < 60 separated by 90 days [10]								45% ACEi & 9% ARB	47%		
US, 1999-2004; 12,065 NHANEs patients; 1324 with stage 3-5 CKD [11]						94%					
US, 2000-2002; 619 patients with CKD (eGFR < 50) [12]								44% ACEi & 13% ARB	16%		
US (FHS offpsring cohort), 1998-2001; 3258 patients; 281 with CKD[13]								37% ACEi	57%[6]		
UK, 2007-2013; 93,406 patients with eGFR < 60; 12,988 had 2 eGFRs < 60 within 3 months [14]	25%[7]	36%[8]									

Population & Setting	Quality of Care Indicators (see Table 1 for definitions)										
	1	2	3	4	5	6	7	8	9	10	11
	Repeat eGFR	f/u ACR	Repeat ACR	SCr monitor	ACR monitor	No NSAID	No ACEi & ARB	ACEi/ ARB	Statin	ACEi/ ARB f/u SCr or K	
UK, 2012; 12,011 patients with 2 eGFRs < 60 [15]						89%					
UK, 2010; 165,942 patients with stage 3-5 CKD [16]							98%	52%	49%		
UK, [date unknown, prior to 2011]; 148 primary care physicians [17]								79%			
UK, 2000-2003; 74,096 patients (not all had CKD) [18]										59%	
UK, 1999-2003; 38,262 patients with sCr values [19]								38 - 44%[1]			
Italy, 2006-2011; 1989 patients with CKD [20]						64%					
Italy, 2005; 39,525 patients with hypertension; 9043 had eGFR < 60 [21]	14%[9]							73%			
Netherlands, 2012; 4706 patients with diabetes and CKD						97%[10]	96%	78-82%[11]	74%		
Netherlands, 2006; 202 patients with CKD [22]										34%	28%

Population & Setting	Quality of Care Indicators (see Table 1 for definitions)										
	1	2	3	4	5	6	7	8	9	10	11
	Repeat eGFR	f/u ACR	Repeat ACR	SCr monitor	ACR monitor	No NSAID	No ACEi & ARB	ACEi/ ARB	Statin	ACEi/ ARB f/u SCr or K	
Denmark, 1997-2006; 6663 patients on chronic dialysis [23]						64%					
Pakistan, 2004-2005; 267 patients with CKD [24]								71%			
Singapore, 2007-2011; 4734 patients with CKD in 2007 and 10,245 in 2011 [25]								78 - 84%[12]	81 - 87%[12]		
Taiwan, 2010-2011; 3057 participants; 818 with CKD (eGFR < 60) [26]								13% ACEi & 56% ARB	66%		
Australia, 2008; 4966 patients with kidney lab data [27]	28% and 67%[13]							81% and 93%[14]	59% and 68%[15]		
Australia, 2004-2006; 3175 patients (general population; # with CKD not reported) [28]						84%					

[1] Range based on comorbidities
[2] Range based on progression risk
[3] GP correctly identified as having CKD
[4] ACR or proteinuria
[5] Patients on lipid-lowering drug (one of which was statins)
[6] Patients on lipid-lowering drug (did not specify statins)
[7] Among patient with incident CKD identified by labs, patients who were registered as CKD over study period
[8] Among patient with incident CKD identified by labs, patients who had an ACR test over study period
[9] Among patients with CKD based on labs values, patients who had a CKD diagnosis
[10] Among patients with eGFR < 30 L/min/1.73m^2 only

[11] Range based on risk factors: macroalbuminuria versus microalbuminuria and diabetes
[12] Range based on year
[13] Number of patients with CKD stage 3 and stage 4-5, respectively, who were correctly diagnosed by GP
[14] Number of patients with CKD stage 3 and stage 4-5 on a hypertension drug (does not mention ACEi/ ARB specifically)
[15] Number of patients with CKD stage 3 and stage 4-5 on a lipid lowering drug (does not mention statin specifically)

Abbreviations: ACE, Angiotensin Converting Enzyme; ACR, Albumin-to-Creatinine Ratio; ARB, Angiotensin Receptor Blockers; CKD, Chronic Kidney Disease; eGFR, estimated Glomerular Filtration Rate; FH, Framingham Heart Study; f/u, follow-up; K, Potassium; KP, Kaiser Permante; NHANES, National Health and Nutrition Examination Survey; NSAIDs, Non-Steroidal Anti-Inflammatory Drugs; SCr, Serum Creatinine; UK, United Kingdom; US, United States; VA, Veterans Affairs.

Note: We present values descriptively rather than combining statistically using meta-analysis, since study settings and indicator definitions were diverse.

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Appendix 2: Checklist of Recommendations for Reporting of Observational Studies using the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement[50]

	Item No	STROBE items	RECORD items	Reported
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract. (b) Provide in the abstract an informative and balanced summary of what was done and what was found.	(1.1) The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. (1.2) If applicable, the geographic region and time frame within which the study took place should be reported in the title or abstract. (1.3) If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Title & Abstract
Introduction				
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported.		Background
Objectives	3	State specific objectives, including any prespecified hypotheses.		Background
Methods				
Study design	4	Present key elements of study design early in the paper.		Methods – Study Design and Research Setting
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection.		Methods – Study Design and Research Setting & Patients
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. (b) For matched studies, give matching criteria and number of exposed and unexposed.	(6.1) The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. (6.2) Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. (6.3) If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage	6 a) Methods – Patients 6.1 Appendix 3a & 3b

			process, including the number of individuals with linked data at each stage.	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	(7.1) A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Methods – Definitions of Quality Indicators & Statistical Analyses
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group.		Methods – Data Sources & Definitions of Quality Indicators
Bias	9	Describe any efforts to address potential sources of bias.		N/A
Study size	10	Explain how the study size was arrived at.		Results – Patients & Figure 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why.		Methods – Statistical Analyses
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding. (b) Describe any methods used to examine subgroups and interactions. (c) Explain how missing data were addressed. (d) If applicable, explain how loss to follow-up was addressed. (e) Describe any sensitivity analyses.		Methods – Statistical Analyses
Data access and cleaning methods		N/A	(12.1) Authors should describe the extent to which the investigators had access to the database population used to create the study population. (12.2) Authors should provide information on the data cleaning methods used in the study.	Methods – Patients & Figure 1
Linkage		N/A	(12.3) State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	Methods – Data Sources

Results				
Participants	13	(a) Report numbers of individuals at each stage of study--e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed. (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram.	(13.1) Describe in detail the selection of the persons included in the study (i.e., study population selection), including filtering based on data quality, data availability, and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Methods – Patients & Figure 1
Descriptive data	14	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders. (b) Indicate number of participants with missing data for each variable of interest. (c) Summarize follow-up time (e.g. average and total amount).		14 a) & b) Results – Baseline Characteristics & Table 2 14 c) Results – Quality Indicator Performance & eTable 4
Outcome data	15	Report numbers of outcome events or summary measures over time.		Results – Quality Indicator Performance & Table 3
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g. 95% confidence interval). Make clear which confounders were adjusted for and why they were included. (b) Report category boundaries when continuous variables were categorized. (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period.		Results – Quality Indicator Performance & Table 3
Other analyses	17	Report other analyses done (e.g. analyses of subgroups and interactions, and sensitivity analyses).		Results – Quality Indicator Performance & eFigures 1-4
Key results	18	Summarize key results with reference to study objectives.		Discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	(19.1) Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Discussion – Strengths and Limitations

Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.		Discussion
Generalizability	21	Discuss the generalizability (external validity) of the study results.		Discussion
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based.		Declarations – Funding
Accessibility of protocol, raw data, and programming code		N/A	(22.1) Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Declarations – Availability of data and materials

Appendix 3a: Administrative Codes used to Define Chronic Kidney Disease Quality of Care Indicators

Healthcare Measure	Code Type	Codes
Serum Creatinine	OHIP feecode	L065, L067, L068
Albumin-to-Creatinine Test	OHIP feecode	G009, G010, L253, L254
Diabetes	OHIP diagnostic code	250
	ICD-10	E11, E13, E14
Serum Potassium	OHIP feecode	L204

Abbreviations: ICD-10, 10th edition of the Canadian Modified International Classification of Disease system; OHIP, Ontario Health Insurance Plan.

Appendix 3b: Drugs used to Define Chronic Kidney Disease Quality of Care Indicators

Drug Class	Drug Name
ACE Inhibitor	Benazepril Chlorohydrate Benazepril HCL Captopril Cilazapril Cilazapril & Hydrochlorothiazide Enalapril Sodium Fosinopril Fosinopril Sodium Hydrochlorothiazide & Lisinopril Hydrochlorothiazide & Quinapril HCL Hydrochlorothiazide & Ramipril Indapamide & Perindopril Tert.Butylamine Lisinopril Perindopril Tert.Butylamine Quinapril Ramipril Trandolapril
ARB	Amlodipine Besylate & Telmisartan Anastrozole Candesartan Candesartan Cilexetil Candesartan Cilexetil & Hydrochlorothiazide Eprosartan Mesylate Eprosartan Mesylate & Hydrochlorothiazide Hydrochlorothiazide & Irbesartan Hydrochlorothiazide & Losartan Potassium Hydrochlorothiazide & Olmesartan Medoxomil Hydrochlorothiazide & Telmisartan Hydrochlorothiazide & Valsartan Irbesartan Irbesartan & Hydrochlorothiazide Losartan Potassium Olmesartan Medoxomil Telmisartan Valsartan
Statin	Atorvastatin Calcium Cerivastatin Sodium

	Fluvastatin Fluvastatin Sodium Lovastatin Pravastatin Pravastatin Sodium Rosuvastatin Calcium Simvastatin
NSAID	Celecoxib Diclofenac Diclofenac Sodium Diclofenac Sodium & Misoprostol Diflunisal Etodolac Fenoprofen Calcium Floctafenine Flurbiprofen Ibuprofen Indomethacin Ketoprofen Ketorolac Tromethamine Mefenamic Acid Meloxicam Nabumetone Naproxen Naproxen Sodium Oxaprozin Phenylbutazone Piroxicam Rofecoxib Sulindac Tenoxicam Tiaprofenic Acid Tolmetin Sodium Valdecoxib

Abbreviations: ACE, Angiotensin Converting Enzyme; ARB, Angiotensin Receptor Blockers; NSAIDs, Non-Steroidal Anti-Inflammatory Drugs

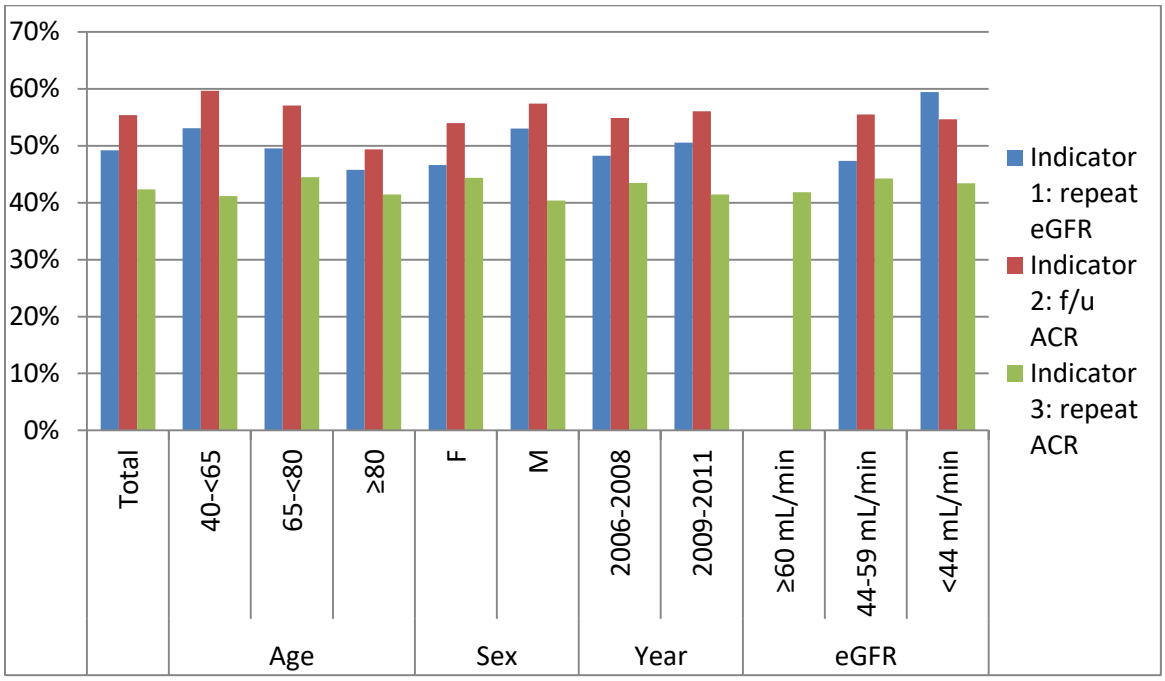
Appendix 4: Distribution of Follow-up Times to Assess Each Indicator (Reported in Years)

Indicator		Mean (SD)	Median (IQR)	Total
Screening/ Recognition of CKD				
1	% of patients with an initial eGFR <60 mL/min/1.73 m^2 who received a repeat serum creatinine test in the following six months.	0.35 (0.17)	0.48 (0.20 – 0.49)	78,713
2	% of patients with an initial eGFR <60 mL/min/1.73 m^2 who received a urine albumin-to-creatinine test in the following six months (including the day of the initial eGFR).	0.26 (0.23)	0.30 (0.00-0.50)	58,398
3	% of patients with an initial ACR >3 mg/mmol who received a repeat urine albumin-to-creatinine test in the following six months.	0.39 (0.15)	0.49 (0.28 – 0.49)	51,028
Monitoring of Kidney Function				
4	% of patients with CKD (based on two eGFR values < 60 mL/min/1.73 m^2) who received a serum creatinine test in the following 18 months.	0.57 (0.46)	0.44 (0.20 – 0.89)	104,728
5	% of patients with CKD who received a urine albumin-to-creatinine test in the following 18 months.	0.85 (0.53)	0.82 (0.35 – 1.5)	156,164
Use of Appropriate Medication				
6	% of patients aged 66 and older with CKD who were not prescribed an NSAID for longer than two weeks.	0.89 (0.26)	1.00 (1.00 – 1.00)	140,450
7	% of patients aged 66 and older with CKD who are not simultaneously receiving both an ACE inhibitor and an ARB.	1.03 (0.50)	1.00 (1.00 – 1.00)	162,418
8	% of patients aged 66 and older with CKD with ACR ≥3 mg/mmol and/ or diabetes who are prescribed an ACE inhibitor or ARB.	0.55 (0.37)	0.54 (0.19 – 0.98)	39,344
9	% of patients 66 to 80 years of age with CKD who received a statin.	0.61 (0.37)	0.70 (0.24 – 1.00)	57,093
Monitoring of ACE inhibitors and ARBs				
11	% of patients aged 66 and older with CKD who received a serum creatinine test 7-30 days after initial ACE inhibitor/ ARB prescription.	0.90 (0.33)	1.08 (0.85 – 1.08)	10,126
10	% of patients aged 66 and older with CKD who received a serum potassium test 7-30 days after initial ACE inhibitor/ ARB prescription.	0.91 (0.32)	1.08 (0.94 – 1.08)	10,263

Abbreviations: ACE, Angiotensin Converting Enzyme; ACR, Albumin-to-Creatinine Ratio; ARB, Angiotensin Receptor Blockers; CKD, Chronic Kidney Disease; eGFR, estimated Glomerular Filtration Rate; NSAIDs, Non-Steroidal Anti-Inflammatory Drugs.

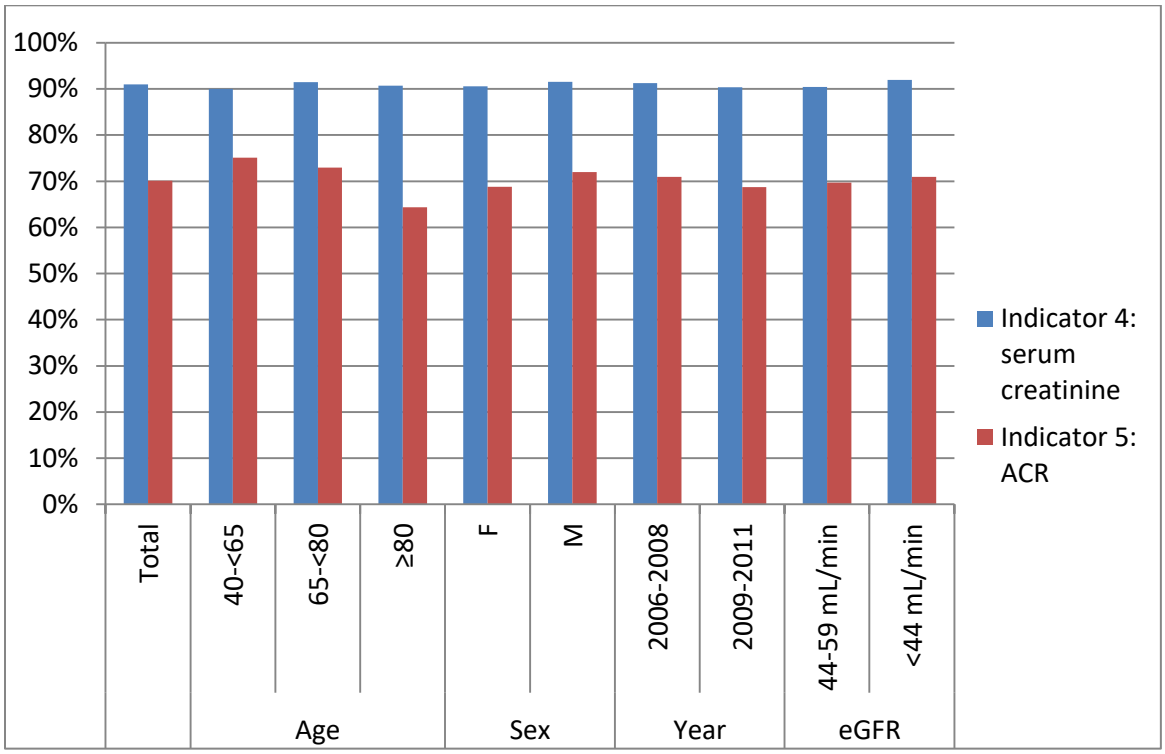
*Note: look-forward period was more than one year for some patients because we followed patients until the end of continuous use of ACE inhibitor or ARB over the entire study period. We did include only ACE inhibitor or ARB prescriptions initiated in the one year following the CKD date.

Appendix 5a: Screening Indicators Stratified by Age, Sex, Cohort Entry Period and Estimated Glomerular Filtration Rate



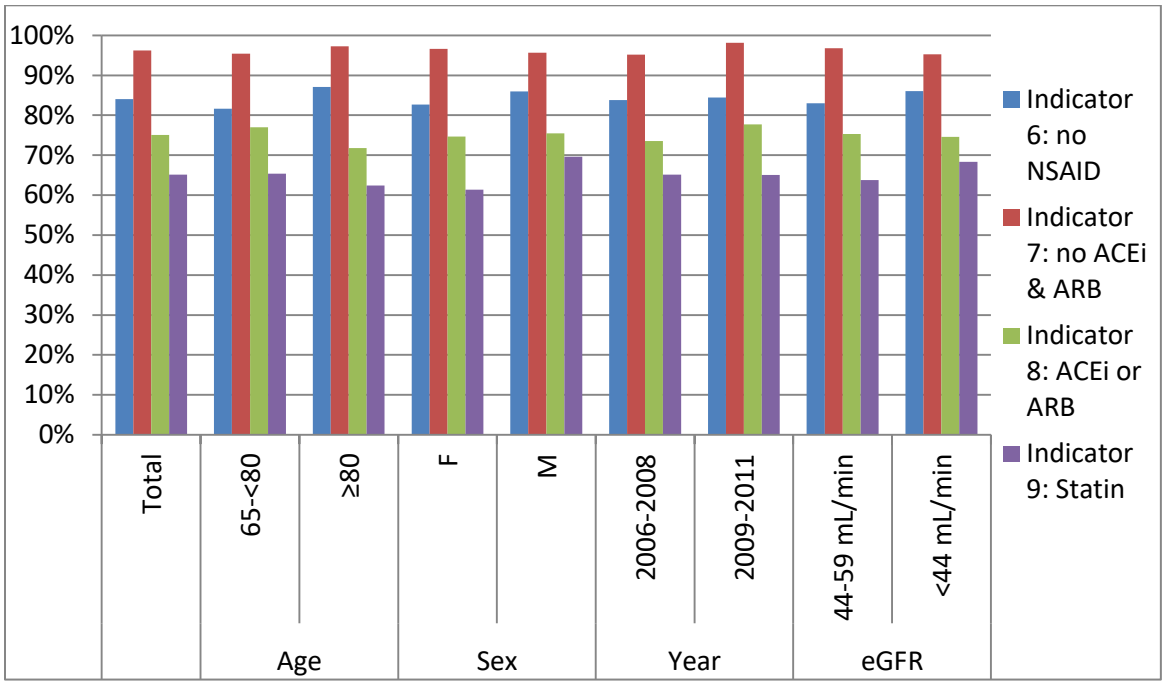
Abbreviations: ACR, Albumin-to-Creatinine Ratio; CKD, Chronic Kidney Disease; eGFR, estimated Glomerular Filtration Rate

Appendix 5b: Kidney Function Monitoring Indicators Stratified by Age, Sex, Cohort Entry Period and Estimated Glomerular Filtration Rate



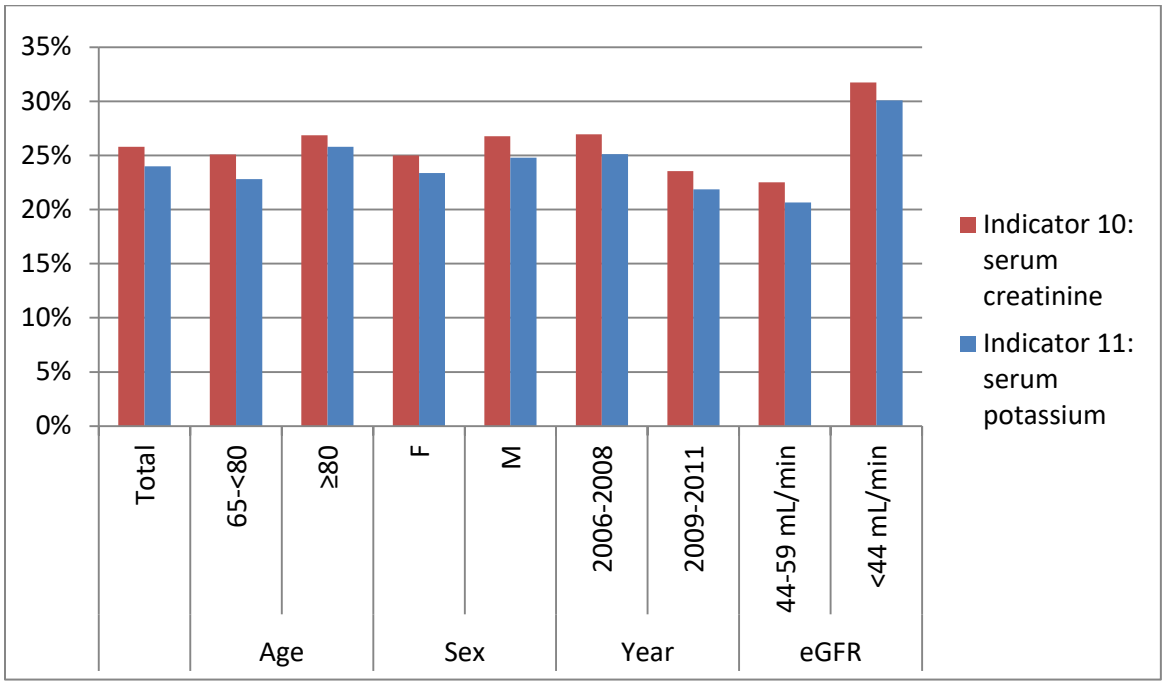
Abbreviations: ACR, Albumin-to-Creatinine Ratio; CKD, Chronic Kidney Disease

Appendix 5c: Prescribing Indicators Stratified by Age, Sex, Cohort Entry Period and Estimated Glomerular Filtration Rate



Abbreviations: ACEi, Angiotensin Converting Enzyme Inhibitor; ARB, Angiotensin Receptor Blockers; CKD, Chronic Kidney Disease; NSAIDs, Non-Steroidal Anti-Inflammatory Drugs

Appendix 5d: Monitoring of ACE Inhibitor or ARB Indicators Stratified by Age, Sex, Cohort Entry Period and Estimated Glomerular Filtration Rate



Abbreviations: ACE, Angiotensin Converting Enzyme; ARB, Angiotensin Receptor Blockers; CKD, Chronic Kidney Disease

3. STUDY 2

Nash DM, Garg AX, Brimble KS, Markle-Reid M. Primary care provider perceptions of enablers and barriers to following guideline-recommended laboratory tests to confirm chronic kidney disease: a qualitative descriptive study. BMC Fam Pract. 2018 Dec 10;19(1):192.

Title: Primary Care Provider Perceptions of Enablers and Barriers to Following Guideline-Recommended Laboratory Tests to Confirm Chronic Kidney Disease: A Qualitative Descriptive Study

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3.1 ABSTRACT

Background: Patients should receive follow-up serum creatinine tests after an initial abnormal result to diagnose chronic kidney disease. However, half of the time this fails to occur in primary care. We interviewed primary care providers to better understand their perceptions of enablers and barriers to following this guideline-recommended care.

Methods: We performed a qualitative descriptive study guided by the Theoretical Domains Framework (TDF), a framework for behavioural change. We used purposeful sampling to recruit primary care providers (physicians and nurse practitioners) based on provider and practice characteristics (rural, solo versus team practice, etc.) from Ontario, Canada. We completed one-on-one interviews with providers using a semi-structured and open-ended interview guide based on the 14 TDF domains. We alternated between data collection and analysis, where we used directed content analysis to identify frequent, important, and conflicting enablers and barriers.

Results: We completed 13 interviews with nine primary care physicians and four nurse practitioners. Nine themes related to the TDF emerged from the data: 1) environmental context and resources, 2) knowledge, 3) memory, attention, and decision processes, 4) beliefs about consequences, 5) goals, 6) social or professional role, 7) behavioural regulation, 8) skills, and 9) optimism. Within these themes, we identified 16 enablers and five barriers. Some enablers included, providers' knowledge on appropriate testing, their motivation to order these tests, and their use of tools and resources to help order follow-up serum creatinine tests. However, providers perceived some barriers including that ordering confirmatory laboratory tests for chronic kidney disease was not always a

priority in regards to other care they wish to provide. Providers also noted that a perceived barrier is patients not going to the laboratory to complete the test.

Conclusions: We identified novel enablers and barriers to primary care providers completing guideline recommended repeat testing for the diagnosis of chronic kidney disease. Similar research is needed to understand the views of patients. These research findings can be used to inform strategies to improve the quality of care.

Keywords: Chronic kidney disease, laboratory tests, qualitative research, primary care, family medicine, theoretical domains framework

Abbreviations

Estimated Glomerular Filtration Rate (eGFR)

Electronic Medical Record (EMR)

Kidney Disease Improving Global Outcomes (KDIGO)

Ontario Renal Network (ORN)

Theoretical Domains Framework (TDF)

Tri-Council Policy Statement 2 (TCPS2)

3.2 BACKGROUND

Approximately 12.5% of all Canadians live with chronic kidney disease [1], which is characterized by a sustained reduction in kidney function and may include significant levels of protein in the urine. Early detection of chronic kidney disease allows healthcare providers to initiate appropriate management to help prevent or slow the patient's progression to kidney failure. Most patients with early stage chronic kidney disease are managed in the primary care setting and are only referred to nephrologists if they have advanced disease or are at increased risk of progression.

International guidelines published in 2013 from Kidney Disease Improving Global Outcomes (KDIGO) recommend that chronic kidney disease should be classified based on estimated glomerular filtration rate (eGFR) and level of albuminuria [2]. These guidelines recommend that patients with an initial eGFR <60 mL/min/1.73 m^2 should have a repeat serum creatinine test within three months to diagnose chronic kidney disease [2]. Although these guidelines are well recognized by nephrologists, primary care providers are generally not aware of them. Additional efforts have been made in several jurisdictions to bridge this gap in primary care. For example, the Ontario Renal Network (ORN), the provincial agency responsible for the delivery of kidney care services in Ontario, Canada, released a flow diagram based on these clinical guidelines to aid primary care providers with appropriate screening, monitoring, management, and referral for chronic kidney disease (the KidneyWise toolkit) [3]. This toolkit provides specific advice for ordering follow-up serum creatinine tests. The ORN has attempted wide

dissemination of this toolkit through national primary care conferences, social media, and integration into electronic medical records (EMRs).

Based on a previous population-based study among Ontario primary care providers, only 49% of patients with initial abnormal eGFR values received a repeat serum creatinine test in the following six months [4]. These findings are consistent with another Ontario study among primary care providers using an EMR [5]. Similarly, studies in other countries have shown that only 14% to 28% of patients with an initial eGFR <60 mL/min/1.73 m^2 have a documented diagnosis for chronic kidney disease [6–9]. It is not clear why this guideline recommendation is not being followed in practice for half of the patients.

Previous literature on evidence-practice gaps in primary care have demonstrated that guideline-based recommendations are generally not being followed in practice due to lack of time and resources, limited relevance of research to practice, and patient-related factors [10–16]. Based on our detailed literature review, we did not find any previous studies on primary care providers' perspectives on the enablers and barriers to completing follow-up serum creatinine tests to confirm chronic kidney disease (Appendix 1). It is not clear if previously identified evidence-practice gaps are relevant to this practice.

There are many different frameworks and theories on clinical practice change and implementation of guidelines [17–19]. We used a robust framework of behavioural change, referred to as the Theoretical Domains Framework (TDF), in our study to shape our research questions, interview guide, and analysis [17,20]. The TDF was developed to help understand why evidence-based guidelines may not be followed in practice and to

help develop strategies to improve implementation of evidence into practice. It is a consensus framework based on 33 behaviour change theories and 128 theoretical constructs to inform implementation research [17]. Based on a validation study of the original TDF, the refined framework includes 14 domains and 84 theoretical constructs [20].

The purpose of this qualitative descriptive study was to use the TDF as a framework to elicit and describe the perceived enablers and barriers to following recommendations for ordering a repeat serum creatinine test after an initial abnormal kidney function test result by Ontario primary care providers.

3.3 METHODS

Study Design

We completed a qualitative descriptive study of primary care providers' perceived enablers and barriers guided by the TDF. This study design was used to provide an in-depth description of enablers and barriers with minimal interpretation of the data [21–23]. We followed the reporting guidelines from the COnsolidated criteria for Reporting Qualitative Research (COREQ) (Appendix 2) [24].

Ethics

In accordance with the Helsinki Declaration, we received research ethics approval from the Hamilton Integrated Research Ethics Board (# 2017-2286). We followed the Tri-Council Policy Statement 2 (TCPS2) guidelines on ethical conduct of qualitative research

[25]. After sharing information about the study, we obtained verbal consent from providers for study participation. We sent the information and consent form by email to the participants if they preferred a copy. Participants received $25 compensation for their time, which was provided after each interview.

Sampling & Recruitment

We used purposeful sampling strategies of maximum variation and snowball sampling to identify information-rich participants. Eligible participants included primary care providers practicing in Ontario who are responsible for ordering laboratory tests (physicians and nurse practitioners).

We used a multi-faceted recruitment strategy. First, we contacted the four main Ontario primary care organizations, which circulated information about our study to their members: 1) Association of Family Health Teams of Ontario, 2) Nurse Practitioners Association of Ontario, 3) Ontario College of Family Physicians, and 4) Association of Ontario Health Centres. These organizations provided our study information to their members either through a regular newsletter, by posting the information on their website, or through an online bulletin. The information provided included a brief explanation of the study and directed people to contact the research team for further information.

Second, we compiled a list of potential participants from the College of Physicians and Surgeons of Ontario and Nurse Practitioners' Association of Ontario websites based on maximum variation selection criteria including rural versus urban clinics, provider sex, number of years practicing, family physician versus nurse

practitioner, size of practice, and team versus individual practices. We contacted these individuals by calling or visiting primary care clinics in the province and briefly explaining the study to the healthcare providers or their administrative staff. We then provided practices with the study information flyer either by email, fax, or in person.

Third, we used snowball sampling by asking individuals to pass along our study information to potential participants to see if they would be interested in our study.

We decided *a priori* that we would recruit at least 13 participants. After the first 10 interviews, we planned on interviewing at least three more participants and completed recruitment when data saturation was reached and no new themes emerged with subsequent interviews [26,27].

Data Collection

One author (DMN; Doctoral student) conducted all one-on-one, semi-structured, open-ended interviews either in person (at the physician office) or by telephone. We developed the interview guide based on the TDF and piloted it prior to the study with two physicians (see Appendix 3). We used the results of the pilot to modify and reframe questions. Example questions included, “How easy or difficult is it for you to regularly order confirmatory tests for chronic kidney disease?” and “What do you think will happen if you do not order confirmatory tests for chronic kidney disease?”. We revised questions slightly throughout the study as the data were analyzed. Based on the semi-structured format of the interviews, we used additional questions and probes to elicit further information or to ask participants to clarify answers. The interviews were audio recorded

and transcribed verbatim. We uploaded the transcripts to NVivo 11 software for assistance with data management when performing the analysis.

We collected demographic and practice information, including provider's age and number of years in practice, to provide some aggregate descriptive information on study participants.

Analysis

We used directed content analysis by using the TDF as a framework to identify and describe the enablers and barriers derived from the data. Content analysis is a qualitative analytic technique where investigators systematically review and describe textual data using codes and themes [28]. Directed content analysis is both a deductive and an inductive analytic approach where an existing theory or framework is used to help guide the analysis and to generate initial concepts and themes [28]. Using this approach, we mapped the data to the 14 TDF constructs to help us identify enablers and barriers to guideline adherence for repeat serum creatinine testing to diagnose chronic kidney disease [17,20]. We also identified any emerging themes from the data that did not fit into any of the TDF constructs.

The analysis was an iterative process, where we alternated between data collection and analysis. This allowed interview questions for subsequent data collection to be revised and also allowed us to determine when data saturation was reached.

We listened to the audio-recordings shortly after each interview and read through the transcripts to correct any errors in transcription and to fully immerse ourselves in the data.

The coding and broader themes were based on the TDF domains. We practiced investigator triangulation to increase credibility in research findings, where both DMN and MMR independently coded the first two interview transcripts, and compared coding to discuss agreement or disagreement. DMN completed the coding of the remaining transcripts independently, but with regular meetings with MMR to review coding progress. Any disagreements were resolved by consensus. We reviewed the transcripts from each interview and assigned initial codes based on the TDF domains to each data item, which typically included one to three sentences.

In the next phase of the analysis, we created sub themes within each broader domain. We then defined, refined and named these sub themes within the codebook, which was used to guide the remaining analysis, and revised throughout the study to reflect emerging themes. Finally, we identified the relevant TDF domains and sub themes by focussing only on the frequent, conflicting, or important themes (i.e. strong beliefs even if they were not as common across the participants).

Throughout the study, we practiced bracketing, which is the ability to separate our own values and opinions from influencing the participants' responses or our interpretation of the results. This is especially important in qualitative research, since the findings are subjective and based on interpretation by the researchers. To ensure credibility and confirmability of findings, DMN kept a reflective journal throughout the research process

to recognize, document, and try to separate any assumptions that may have influenced the research. To ensure credibility of research findings, we also used peer debriefing by meeting with other experienced qualitative researchers from the Ottawa Hospital Research Institute who are familiar with the TDF, but who were not involved in our study. We discussed and confirmed preliminary findings that emerged from the data after completing nine interviews. Finally, we kept a detailed audit trail including the initial study protocol, DMN's reflective journal, audio recordings of the interviews, transcription files of the interviews, and minutes from research team meetings.

3.4 RESULTS

Characteristics of the Study Participants

In total, we completed 13 interviews with 13 individual participants. We reached data saturation after the 10th interview, since no new themes emerged from interviews with participants 11 to 13. Nine out of 13 participants were female and the average age was 46 years. Nine participants were primary care physicians and the remaining four participants were nurse practitioners (see Table 1).

Relevant TDF Domains

Themes emerging from the data reflected nine of the TDF domains: 1) environmental context and resources, 2) knowledge, 3) memory, attention and decision processes, 4) beliefs about consequences, 5) goals, 6) social or professional role, 7)

behavioural regulation, 8) skills, and 9) optimism (see Table 2). In addition to these TDF themes, another theme emerged on completing laboratory tests/ patient factors.

Identified TDF Enablers

Among the nine TDF themes, we identified 16 enablers perceived by primary care providers to ordering repeat serum creatinine tests (see Table 2). The majority of providers were aware of guidelines for ordering a repeat serum creatinine test and most had a positive opinion about using clinical guidelines to inform behaviour and decision-making (*knowledge*). For example: *"I don't think [guidelines] should determine [behaviour], but they should definitely guide it and direct it because it's, again, research based and trying to follow that."* The most commonly used clinical guidelines were for diabetes or the implementation of KDIGO chronic kidney disease guidelines in the ORN's KidneyWise toolkit (*environmental context and resources*). For example:

> *"I think that the algorithm approach is actually relatively simple as opposed to a lot of the other guidelines out there that have algorithms that are about three hundred things on a diagram and then having an application for it is useful. The KidneyWise application is actually quite useful."*

Although not all providers were aware of guidelines for ordering repeat serum creatinine tests, the majority still had the knowledge of when they should be ordering these tests (*knowledge*). For example:

> *"Let's just say I don't know anything about any guidelines. I have a practice that I do, that I believe is correct, so we'll see what happens there."* and *"Actually*

there's one today that just popped up that his glomerular filtration rate dropped like from 70 to 50 which is below normal, so I'm going to repeat it in three months."

Furthermore, providers described that they would refer to guidelines when needed and then tailor the recommendations to the specific patient and their clinical presentation in order to decide when they should order confirmatory tests for chronic kidney disease (*environmental context and resources; memory, attention and decision processes*). For example:

"So usually the first thing if I get an abnormal creatinine or estimated glomerular filtration rate or positive albumin-to-creatinine ratio then it's to, kind of, look and see, okay, is this something new for this person or is this long-standing, is it getting worse, is it stable, is there something else going on, do they have a urinary tract infection… like, something that may account for the finding. If it's something that's completely new then, absolutely, it's repeated."

Besides using clinical guidelines, providers frequently described the use of internal clinic resources to help decide when or if to order a repeat serum creatinine test (*environmental context and resources*). Many providers described the use of support staff (i.e. clerical staff or nurses) to follow up with patients about a repeat serum creatinine test. For example: *"I can just send tasks to certain nurses or support staff just to follow back up with them and ask them to order whatever I need to be done."* Even though providers agreed that having support staff would be helpful, not all providers had

available support staff to assist with ordering laboratory tests or to follow-up with patients (*environmental context and resources*). For example:

> *"If the world was a perfect place some of this stuff could be off loaded to either a nurse or a nurse practitioner that I work with but the world is not a perfect place and we're all just too busy."*

Providers frequently described using different features in their EMRs to help decide whether or not to order laboratory tests or to remind themselves to order a follow-up test (*environmental context and resources; memory, attention and decision processes*). For example: *"The electronic medical record that allows me to kind of track… laboratory results of creatinines over time, is something that helps me determine whether or not I need to do a confirmatory test."* A couple providers also mentioned that having chronic disease registries (mostly for diabetes) could be used to help keep track of patients who may require a follow-up serum creatinine test. However, they mentioned that these registries generally require the help of support staff (who may or may not be available) to manage and track when patients need certain laboratory tests.

Many providers agreed that ordering a repeat serum creatinine test is a priority and helps to prevent potential adverse consequences for the patients (*goals*; *beliefs about consequences*). For example:

> *"You've just got to focus in on one or two different things, and sometimes the chronic kidney disease could get lost in transition. But usually it's incorporated, but that would be the most likely."* and *"One [consequence] is that it continues to go up, and I miss that they're going into much worse renal failure. Another is that*

I give them things that are more toxic, or that are toxic to an already compromised kidney. Those would be the biggest ones."

Providers also agreed that the benefits of ordering these tests outweigh the costs to the healthcare system (*beliefs about consequences*). For example: *"Yes, because it'll cost a lot more if [their kidney function] declines because we didn't check it."*

Overall, providers were generally optimistic about ordering follow-up laboratory tests for chronic kidney disease and were motivated to do so (*optimism; goals*). For example: "*Like there are no concerns about ordering any of these tests."* and *"... I try very hard, because I mean, kidneys are pretty important, right?"*

All participants agreed that ordering a follow-up serum creatinine test to confirm chronic kidney disease is part of their role as primary care providers (*social or professional role*). For example: *"Physicians have to be the ones in Ontario signing blood work requisitions, nurse practitioners and physicians."* Some participants described components of their professional role that enable them to order a repeat serum creatinine test. For example:

"As a nurse practitioner I'm allowed a little bit more time so it makes it a little easier, so I try and provide as much health teaching to the patient and write it on the lab slip when I want them to check it."

Identified TDF Barriers

We identified five barriers perceived by primary care providers to ordering a repeat serum creatinine test to diagnose chronic kidney disease (see Table 2). There were

some conflicting perspectives on views of clinical guidelines where some providers had more pessimistic views (*knowledge*). For example:

> *"I'm going to assume that [guidelines] are evidence based or at least partially evidence based as much as guidelines can be because if you look at those guidelines in general they're about maximally 14% evidence based and the rest is opinion, so I assume that they are approximately the same as every other guideline."*

Some providers did not perceive that it was a priority to order a repeat serum creatinine test relative to other competing priorities in primary care (*goals*). For example:

> *"So I'll tell you what, we have 49 diseases that we deal with in family medicine. Kidneys are one small one, and there's very little to do with that repeat creatinine. There's nothing that changes. So is it a priority? No. There are many other things that are higher priority."*

Providers also described that sometimes they forget to order the repeat testing (*memory, attention and decision processes*), but many mentioned that using the EMR as a resource generally helps to prevent forgetting (*environmental context and resources*). For example:

> *"I think cognitive overload probably plays a part in everything that we do every day and it's a matter of sometimes things just get forgotten."* and *"…I guess once upon a time for me it would have been remembering when it was due. But electronic medical records make it that much easier because you can send yourself little reminders."*

Even though the majority of providers agreed that there are significant clinical consequences for the patients if follow-up laboratory tests are not ordered, a few providers perceived that waiting longer to confirm the initial test result would not change the care they provide for the patient (*beliefs about consequences*). For example:

> *"You know, it's nice to initiate in the workup once they are confirmed [chronic kidney disease] a little bit earlier, but if it has to wait until a year, I don't know that it makes a significant difference, 'cause patients usually present on an annual basis for blood work. Or that's their expectation. So sometimes you only have the chance to repeat it a year later."*

Some providers described components of their professional role that prohibit them from always ordering follow-up laboratory tests (*social or professional role*). For example, providers who work in a family health team described the following: *"…because they're multiple providers… it may be something that someone else has already investigated."*

Other Factors Influencing Laboratory Test Completion

The providers in our study had perceived some patient barriers to completing repeat serum creatinine testing that did not fit within any of the TDF domains. For example, the most prevalent barrier identified was patient compliance (*completing laboratory tests/ patient factors*). Some providers described using communication skills with the patients to explain the importance of getting the laboratory test done, which they perceived helps to improve patient compliance (*skills*). For example: *"So, you know, we*

usually tell them that, no, we need to repeat this because your renal function, we need to make sure your kidneys are good. And then … they're on board."

In addition, providers described other actions that they take to help improve patient compliance in completing laboratory tests when ordered (*behavioural regulation*). For example:

> *"Providing more follow-up and making sure, again, tests are being done as asked of the patient just to make sure they are. So having maybe more tasks sent to myself reminding myself that things have been ordered, to recheck that."* and *"Well, one thing that I will tell you is that I do not file the abnormal test into the patient's chart until I am sure that the patient actually is aware of the abnormal result."*

Providers also mention laboratory factors which may influence whether or not the test is ordered, and ultimately if the patients complete the test (*completing laboratory tests/ patient factors*). For example: *"We used to have a lab in our family practice unit, right in the same building and that really was helpful for our patients in terms of any sort of laboratory investigations, but yeah."*

3.5 DISCUSSION

Using a comprehensive framework of behaviour change to guide our analysis, we identified 16 enablers and five barriers perceived by providers for ordering repeat serum creatinine tests to diagnose chronic kidney disease. We found that there was an interaction between many of the TDF domains. For example, healthcare providers

generally know what they should be doing (*knowledge*), are motivated to do so (*goals*), have the tools and resources required to perform the behaviour (*environmental context and resources*), and use both the information and tools to make an informed decision on whether or not to order a repeat serum creatinine test (*memory, attention and decision processes*). However, ordering follow-up serum creatinine tests was not always perceived as a priority (*goals*) or as directly influencing patient outcomes (*beliefs about consequences*), and might sometimes be forgotten (*memory, attention and decision processes*).

Based on our comprehensive literature search, this is the first qualitative study to assess the enablers and barriers perceived by primary care providers for the behaviour of ordering repeat serum creatinine tests to confirm a chronic kidney disease diagnosis. We found novel enablers and barriers that have not been reported in previous studies related to chronic kidney disease care or laboratory ordering in general, including the following enablers: making a deliberate decision and being aware of clinical consequences; and barriers: forgetting to order tests and prioritizing care goals.

Unlike other studies on guideline adherence for chronic kidney disease care, we found that providers are generally aware of guidelines or at least know that they should be ordering repeat serum creatinine tests to confirm chronic kidney disease [29–32]. Previous studies have shown low awareness of national (U.S.) and international guidelines specifically for chronic kidney disease. In contrast, we were interested in participants' awareness of any guidelines for confirming chronic kidney disease with

repeat serum creatinine testing [2,33]. As such, our participants were generally more aware of diabetes guidelines and a provincial kidney algorithm.

Although the majority of participants in our study had positive attitudes towards clinical guidelines for ordering follow-up serum creatinine tests, there were some dissenting views perceiving that these guidelines lacked clinical evidence. Estrella et al. (2003) conducted a survey with healthcare providers and also found that many participants did not perceive chronic kidney disease guidelines to be evidence-based [34].

Consistent with our study findings, previous studies have found that primary care providers perceive laboratory tests to be useful in assessing kidney function [31,35]. However, we found that even though providers were generally motivated to order a repeat serum creatinine test and perceived this to be important, it was not always a priority. Furthermore, we identified another barrier where some participants perceived that the care they provide for the patient will not change if they do not order follow-up serum creatinine tests in a timely manner. This result is consistent with findings from Crinson et al. (2010), who performed focus groups with primary care providers on their perceptions of chronic kidney disease management [35].

Similar to our findings, previous studies have also shown that the use of internal resources are enablers to caring for patients with chronic kidney disease and ordering laboratory tests. For example, providers generally rely on support staff and use electronic medical records to provide better patient care [36–39].

Finally, previous studies on primary care providers' perceived enablers and barriers to ordering laboratory tests in general have also identified that a barrier is patients

not completing the laboratory test [37,40]. A mixed methods study on patient perceived barriers to not completing a laboratory test after initiating a new medication that required monitoring included barriers of forgetting or competing demands [41]. Since our study only included the primary care provider perspective, we cannot make any conclusions about the applicability of these patient-specified barriers to completing a repeat serum creatinine test. Additional research is needed to further investigate these findings.

Strengths and Limitations

We used strategies suggested by Guba (1981) as outlined in our methods section to ensure rigour in our qualitative study [42]. This helps to increase the credibility, dependability, confirmability, and transferability of our study findings.

Another strength of our study is using the TDF to help frame our research, since it is comprehensive, validated, and has been successfully used in previous research on guideline implementation [17,20]. Furthermore, the TDF also includes clearly defined domains that were applicable to our setting. A limitation of using a framework to guide our study is that we may have missed themes that were not captured through the TDF.

The findings from our study are transferable to other settings, for instance, primary care providers who work in similar primary healthcare settings across Canada. Based on the maximum variation sampling criteria that we applied, and our multi-faceted recruitment strategies, our findings likely apply to primary care physicians and nurse practitioners, female and male providers, urban and rural clinic settings (including Northern Ontario), practices of varying sizes, different types of practice models, and

providers who have been practicing for different lengths of time. Even though we included both urban and rural primary care providers in our study, the majority of rural providers were nurse practitioners. This may have limited the perception specifically of rural primary care physicians. Furthermore, the majority of the participants in our study practiced in a family health team or a family health organization, thereby limiting the perceptions captured by solo-practicing providers. Previous literature has shown that providers perceive lack of effective reminders or tools to track laboratory tests in the EMRs is a barrier to ordering tests [37–39]. All participants in our study described that they used an EMR to order tests and most described this as an enabler. Therefore, our findings may not apply to primary care providers who do not use an EMR in practice.

Study Implications

This research has implications on the care of patients with chronic kidney disease in the primary care setting. The results of our study can be used to inform future interventions to help improve care regarding repeat serum creatinine tests to diagnose chronic kidney disease.

Future strategies to improve confirmatory laboratory test ordering for chronic kidney disease need to be multi-factorial since many components of the TDF apply to this behaviour. By mapping the relevant TDF domains to the Behaviour Change Wheel, we can identify interventions that may help to improve adherence to this behaviour [20,43]. For example, since we showed that an enabler is use of tools within EMRs, we could use an environmental restructuring intervention to improve reminders or prompts within the

EMRs to order follow-up laboratory tests. As another example, we could use a persuasion intervention such as presenting convincing yet factual information on the importance of ordering confirmatory tests to delay disease progression. This would help overcome the perceived barriers of ordering repeat serum creatinine tests being a low priority and that there is little harm in delaying confirmatory testing.

The findings from this research can potentially be generalized to guideline-recommendations in primary care beyond chronic kidney disease. For instance, some of the enablers and barriers identified in this study might be applicable to confirmatory testing for hypothyroidism [44]. However, future research is needed to explore the applicability of these factors to the implementation of other guidelines in primary care.

Conclusions

Overall, we identified some novel enablers and barriers perceived by primary care providers in regards to ordering repeat serum creatinine tests to diagnose chronic kidney disease. The majority of participants know that they should be ordering these tests, and are generally motivated, and have the required resources to do so. However, some providers perceived that ordering a repeat serum creatinine test would not change the care they provide and it may not always be a priority to the provider or the patient. Providers also perceived that there may be other contributing factors beyond their control, such as patients not going to the laboratory to complete these tests. Future qualitative research with patients as the participants is needed to confirm and further investigate this finding.

Declarations

Ethics approval and consent to participate: We received ethics approval for this study from the Hamilton Integrated Research Ethics Board (# 2017-2286). Verbal informed consent from the participants was required for study participation.

Consent for publication: Not applicable.

Availability of data and material: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: No authors have declared any competing interests.

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Authors' contributions: DMN and AXG were responsible for study conception. DMN and MMR were responsible for the study design, analysis and interpretation of the results. DMN, MMR, AXG and KSB provided feedback on the study design and findings. DMN, MMR, AXG and KSB reviewed and approved of the manuscript.

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Authors' information (optional): DMN is a female doctoral student with qualitative research course experience but no previous qualitative interview experience. MMR is a nurse with training in qualitative research (PhD). AXG and SB are nephrologists and clinician investigators.

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3.7 TABLES & FIGURES

Table 1. Demographic and Practice Characteristics for the 13 Study Participants

Characteristics	Percentage/ Mean	Standard Deviation	Range (min – max)
Gender (% female)	69.2%		
Age (years)	45.8	9.2	29-59
Primary care physician or nurse practitioner (% primary care physician)	69.2%		
Number of years practicing	15.3	9.9	1-32
Medical school/ nurse practitioner program location (% Canada)	92.3%		
Practice location (% urban)	69.2%		
Practice type (% family health team/ family health group)	92.3%		
Approximate number of patients rostered/ in the practice	2,248	3,219	200-12,500

Table 2. Relevant Theoretical Domains Framework (TDF) Themes and Sub-themes Identified as Enablers or Barriers

Domain/ Theme	Sub-theme	Relevance	Enabler/ Barrier
Environmental context and resources	Using EMR tools	Frequent	Enabler
	Referring to guidelines	Frequent	Enabler
	Depending on support staff	Frequent	Enabler
Knowledge	Being aware of guidelines	Conflicting	Enabler
	Having a positive attitude toward guidelines	Conflicting	Enabler & Barrier
	Knowing what to do	Frequent	Enabler
Memory, attention and decision processes	Making a deliberate decision	Frequent	Enabler
	Forgetting	Important	Barrier
Beliefs about consequences	Being aware of clinical consequences	Frequent	Enabler
	Perceived low risk in delaying confirmatory test	Important	Barrier
	Weighing the costs and benefits	Frequent	Enabler
Goals	Prioritizing care goals	Conflicting	Enabler & Barrier
	Recognizing the importance	Frequent	Enabler
Social or professional role	Claiming responsibility	Frequent	Enabler
	Identifying practice type or role influences	Frequent	Enabler & Barrier
Behavioural regulation	Taking ownership of action	Frequent	Enabler
Skills	Demonstrating communication skills	Important	Enabler
Optimism	Having a positive attitude	Frequent	Enabler
N/A**	Completing laboratory tests/ patient factors	Frequent	Barrier

**This was not one of the TDF domains but was considered a relevant theme.

3.8 APPENDICES

Appendix 1: Literature review of previous relevant qualitative research studies

Reference	Study Objective	Brief Methodology	Summary of Results
Qualitative Research on Implementing Guidelines for Chronic Kidney Disease in Primary Care			
Lo et al., 2016 [1]	To explore how the care for patients with CKD and diabetes can be improved according to primary and tertiary care providers.	Qualitative study, which included a combination of focus groups with care providers and interviews with the unit heads.	Sixty-five primary and tertiary care providers participated. Important factors included: lack of patient self-management, poor access to tertiary care, poor coordination and integration across primary and tertiary care, reactive approach to care where focus is on treatment rather than prevention, and need for more participation in quality improvement activities.
Vest et al., 2015 [2]	To understand barriers to guideline implementation for patients with CKD.	Mixed methods study of a cluster randomized trial with an embedded qualitative component. Semi-structured interviews with physicians.	Themes were organized into the components of the Normalization Process Theory: coherence (some physicians not aware of guidelines – or some of the aspects – for CKD, mostly used guidelines to help diagnose, lack of continuing education and challenge of keeping up with changing guidelines, some physicians do not like to give their patients the label of CKD or rather refer to the nephrologist to diagnose), cognitive participation (challenges with population health management and keeping up with all the different initiatives; challenge of unmotivated or

			non-adherent patients), collective action (limited time and resources/ staff, and competing demands) and reflexive monitoring (do not currently receive audit and feedback reports for CKD, data collection and management challenging and time consuming).
Blakeman et al., 2012 [3]	To identify processes underpinning the implementation of CKD management in primary care.	Qualitative study following the Normalization Process Theory. Interviews with PCPs and nurses from 19 participating sites from another study.	Three main themes emerged all around the anxiety associated with disclosure of CKD with patients: 1) tensions related to identifying and discussing CKD in older patients or those with early CKD, 2) embedding early-stage CKD within vascular care, and 3) distribution of work within the practice team. These research findings suggested that the current approach to management of early-stage CKD in primary care may miss opportunities to address susceptibility to renal damage, improve self-management of cardiac conditions, and improve the management of multi-morbidity.
Greer et al., 2012 [4]	To identify PCPs' perceived barriers of educating patients about CKD.	Qualitative study using focus groups with PCPs. Analysis used methods from grounded theory.	Eighteen PCPs participated in 3 focus groups. Six main barriers emerged: 1) Patients not aware of CKD or not recognizing it as a medical problem, 2) PCPs not perceiving CKD as a distinct medical condition, 3) PCPs lack of knowledge to properly educate patients, 4) Do not want to overwhelm patients

			with a new diagnosis, 5) Time constraints with patients (no time for education), and 6) Lack of available educational resources.
Crinson et al., 2010 [5]	To assess the perspectives of PCPs on the new UK guidelines for CKD.	Qualitative diagnostic analysis using focus groups to inform the intervention of a clinical trial. Purposive sampling of 5 of the 70 practices that had agreed to participate in the clinical trial.	Eight themes emerged: 1. General responses to CKD 2. Issues surrounding use of the eGFR measures 3. Labeling issues: belief that kidney disease part of normal aging process 4. Issues surrounding giving a CKD diagnosis 5. Issues surrounding the management of blood pressure in CKD 6. Patient self-management and compliance issues in relation to meeting blood pressure targets 7. Nephrology referral issues 8. Educational requirements of practice regarding CKD
Feldstein et al., 2010 [6]	To understand the barriers and facilitators to care for CKD in primary care.	Qualitative study which included initial interviews to develop broad questions to be used for focus groups with PCPs and nurse practitioners.	There were 26 participating care providers in 5 focus groups. Barriers and facilitators included: guideline and patient factors (guidelines not flexible, patients not self-managing, patient costs and dealing with multiple providers), PCP factors (lack of time, lack of knowledge and attitudes about guidelines), system factors (lack of decision support tools, low physician autonomy, poor access to information,

			systems made for acute not chronic diseases). Facilitators included clear and specific guidelines, awareness of guidelines, clinical decision support tools, clinic support staff and easy access to patient information.
Williams et al., 2008 [7]	To determine factors associated with adherence to multiple medications for patients with CKD and diabetes.	Descriptive exploratory qualitative study including structured interviews with patients who have CKD and diabetes and focus groups with physicians.	Results included themes of: 1) purposeful action (patients did not have a strong intention to take medications, which went against what physicians thought); 2) perceived need (patients did not think they needed all medications or know why they were taking them); 3) perceived effectiveness (patients did not perceive all their medications to be effective); 4) medication safety (medications causing side effects according to patients, physicians think they may be over-reacting in most cases); 5) access (patients who forgot to refill prescriptions, although pharmacists helped prevent this; other access barriers of costs, lack of transportation, physical symptoms); 6) routine (patients disliked change to their medication routines); 7) remembering (patients forgetting to take medications; physicians noted that poor mental health was a barrier); 8) feedback (physician-patient relationship was

			important to adherence; patients lacked knowledge about what medications were for; some patients used prompts to remember to take pills).
Fox et al., 2006 [8]	To assess PCPs' knowledge of CKD and uptake of Kidney Disease Outcome Quality Initiative (K/DOQI) guidelines.	Qualitative study using semi-structured interviews and surveys with PCPs.	Ten PCPs participated in the study. Five main themes emerged: 1) lack of awareness of K/DOQI guidelines (none of physicians reported being aware of or using guidelines), 2) suggestions for more CKD guidelines (strongly believed in following guidelines, especially for hypertension and diabetes but not for CKD), 3) use of outdated approaches (using serum creatinine rather than eGFR and proteinuria to diagnosis and monitor), 4) inconsistent methods to treat comorbidities, and 5) uncertainty about timing for nephrology referral (have own rules on when to refer and most reported difficulty in communicating with nephrologists and sharing care of patient).
Research on Reasons for Care Gaps Regarding Laboratory Test Ordering (non-Chronic Kidney Disease)			
Litchfield et al., 2014 [9]	To understand PCPs' reasons for ordering liver function laboratory tests.	Prospective study with interviews.	Factors categorized into: 1) Internal: general attitudes and efficacy of ordering liver function tests and 2) External: social influence and test characteristics. This may take precedence over internal/ clinical characteristics.

Menon et al., 2014 [10]	To identify factors associated with facilities who had low or high missed test results in the Veterans Affairs electronic medical record system.	Mixed-methods evaluation, which used previous surveys to classify facilities as low or high risk and qualitative interviews with these facilities.	Forty facilities participated (20 low risk and 20 high risk). High risk scenarios for missed tests included: tests ordered by trainees were sometimes missed if laboratories only notified the ordering physician and not an attending physician as well; assignment of surrogates when physicians were on extended vacation/ leave where surrogates were not always assigned or did not always act on the test result; patients may not have been assigned to a PCP in the electronic medical record system.
West et al., 2014 [11]	To understand the perceived care gaps for laboratory management in practice.	Survey to clinicians and staff in Colorado primary care practices.	There were 384 completed surveys from 21 practices. Barriers included human error and communication issues during handoff, difficulty with sorting through laboratory results, patient no shows to laboratories, and outdated contact information when trying to notify patients.
Goldman et al., 2010 [12]	To understand physicians' perspectives on laboratory monitoring for drugs.	Qualitative study using focus groups with physicians.	Twenty-nine physicians participated (20 internal medicine physicians or PCPs and 9 specialists). The participants agreed that laboratory monitoring was an important and time-consuming (and non-reimbursed) part of their practice. They were surprised by the number of errors that had been reported in the literature but recognized

			that errors sometimes do occur. Barriers included: uncertainty about who is responsible for ordering a laboratory test (i.e. when specialist prescribes it); uncertainty about when to order laboratory tests (i.e. for drugs perceived as low-risk); absence of automated reminders to keep track of laboratory test ordering; patients not completing laboratory tests that were ordered. A facilitator included workflow procedures (i.e. patients coming into the office each month to receive new prescription) and being able to tailor electronic medical record alerts for their practice (e.g., certain follow-up intervals for drugs). There were some concerns about alert fatigue or the number of clicks required to deal with alerts.
Elder et al., 2009 [13]	To understand laboratory test result management systems in family physician offices and to understand factors for optimal management.	Multi-method study using observations, interviews and surveys among 4 purposefully selected family medicine clinics.	Some themes that emerged included: 1) Safety awareness (leadership communicates and demonstrates commitment to safety and quality care; communication between staff and physicians on safety and quality care; teamwork; procedures and protocols for managing tests exist and are kept up-to-date); 2) Adoption of technology (electronic medical records incorporate office

			management tasks; digital ordering of laboratory tests and for receiving results; electronic medical records generate communication of laboratory results to patients; return of laboratory results is an automated step in the electronic medical records). Having technology was not a prerequisite for better laboratory management, rather having safety awareness and good communication in sites without electronic medical record technology still showed optimal management strategies.
Parker et al., 2008 [14]	To understand barriers and enablers to adhering to the national cholesterol guidelines in Rhode Island.	Qualitative study including 9 focus groups with physicians.	Summarized results only focus on enablers and barriers to laboratory tests from this study. Fifty primary care physicians participated. Barriers included reimbursement issues for cholesterol screening and management and lack of reminder systems and the cost of informing patients about their laboratory results. Enablers included technologies to rapidly test for cholesterol levels in practice and reminders with point of care guidelines through electronic medical records to assess cholesterol levels.

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Appendix 2: Consolidated criteria for reporting qualitative research (COREQ)

Guide description	Guide questions	Where reported/ Answers
Domain 1: Research team and reflexivity		
Personal characteristics		
1. Interviewer/ facilitator	Which author/s conducted the interview or focus group?	Data Collection
2. Credentials	What were the researcher's credentials? E.g. PhD, MD	Data Collection
3. Occupation	What was their occupation at the time of the study?	Data Collection; Authors' Information
4. Gender	Was the researcher male or female?	Authors' Information
5. Experience and training	What experience or training did the researcher have?	Authors' Information
Relationship with participants		
6. Relationship established	Was a relationship established prior to study commencement?	No, participants were not aware of DMN prior to study.
7. Participant knowledge of the interviewer	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	Participants were aware that DMN was a PhD student and the rationale for completing the study.
8. Interviewer characteristics	What characteristics were reported about the interviewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	Participants were aware that DMN's background was epidemiology and that she was a PhD student at McMaster.
Domain 2: study design		
Theoretical framework		
9. Methodological orientation and theory	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	Background & Study Design
Participant selection		
10. Sampling	How were participants selected? e.g. purposive, convenience, consecutive, snowball	Sampling and Recruitment
11. Method of approach	How were participants approached? e.g. face-to-face, telephone, mail,	Sampling and Recruitment

	email	
12. Sample size	How many participants were in the study?	Characteristics of the Study Participants
13. Non-participation	How many people refused to participate or dropped out? Reasons?	No patients dropped out; many patients who were approached did not participate.
Setting		
14. Setting of data collection	Where was the data collected? e.g. home, clinic, workplace	Data Collection
15. Presence of non-participants	Was anyone else present besides the participants and researchers?	No
16. Description of sample	What are the important characteristics of the sample? e.g. demographic data, date	Characteristics of the Study Participants & Table 1
Data collection		
17. Interview guide	Were questions, prompts, guides provided by the authors? Was it pilot tested?	Data Collection & Appendix 3
18. Repeat interviews	Were repeat interviews carried out? If yes, how many?	No
19. Audio/visual recording	Did the research use audio or visual recording to collect the data?	Data Collection
20. Field notes	Were field notes made during and/or after the interview or focus group?	No field notes, but a journal was written by DMN
21. Duration	What was the duration of the interviews or focus group?	Average duration was 17 minutes with a range of 14 to 24 minutes.
22. Data saturation	Was data saturation discussed?	Sampling and Recruitment & Analysis
23. Transcripts returned	Were transcripts returned to participants for comment and/or correction?	No, during the interview the participants were told that they could listen to their audio recordings if they chose to do so.
Domain 3: analysis and findings		
Data analysis		
24. Number of data coders	How many data coders coded the data?	Analysis

25. Description of the coding tree	Did authors provide a description of the coding tree?	Analysis
26. Derivation of themes	Were themes identified in advance or derived from the data?	Analysis
27. Software	What software, if applicable, was used to manage the data?	Data Collection
28. Participant checking	Did participants provide feedback on the findings?	No
Reporting		
29. Quotations presented	Were participant quotations presented to illustrate the themes / findings? Was each quotation identified? e.g. participant number	Identified TDF Enablers & Identified TDF Barriers; participant numbers for each quote were not provided.
30. Data and findings consistent	Was there consistency between the data presented and the findings?	Identified TDF Enablers & Identified TDF Barriers
31. Clarity of major themes	Were major themes clearly presented in the findings?	Relevant TDF Domains & Table 2

Appendix 3: Interview Guide Questions

Date and time of interview:	
Name of interviewee:	
Name of assistant interviewee:	

[Introducing study]
Thank you for taking time out of your busy schedule to participate in our research study. The purpose of this study is to try and understand the factors that influence whether primary care providers follow guidelines for confirmatory laboratory tests after identifying initial abnormal kidney function to confirm if a patient has chronic kidney disease (serum creatinine, or eGFR).
Please feel free to ask us any questions about the study before we begin. Also, please remember that participation in this study is voluntary. If you would like to end the interview at any time, please do not hesitate to do so.

[Questions about demographics and practice information]
First, I'd like to ask you a couple questions about yourself, your practice and your patients:

Gender	
Primary care physician or nurse practitioner	
May I ask your age?	
How many years have you been practicing?	
Did you go to medical school [the NP program] in Canada or elsewhere? And if so, where?	
Rural/ urban practice location	
Team or individual practice type	
Approximate # of patients in practice/ rostered	

[Background "nature of behaviour"]: I'm not a clinician, but I am aware that there may be different processes by which laboratory tests are ordered in each practice. Can you please walk me through the process by which you order laboratory tests in your practice?

[Questions based on the Theoretical Domains Framework]
Now, I'm going to ask you some specific questions about confirmatory laboratory tests for chronic kidney disease. By this, I mean situations where you find an initial low eGFR and you order follow-up tests to confirm a diagnosis of chronic kidney disease.
There are no right or wrong answers. And some questions might seem repetitive, but these questions are based on behavioural theories to help understand which of these aspects apply to the current situation.

- K – Are you aware of guidelines for confirmatory tests for CKD?
- K – How familiar are you with these guidelines [alternative question: do you know what these guidelines recommend?]

- K – How did you hear about these guidelines? Do you think they are evidence-based?

- G – Do these guidelines conflict with other guidelines that may exist (for example, other diseases, kidney guidelines for other regions)?

- I – Do you intend/ want to order confirmatory tests for CKD?

- S – Are there any techniques or skills that you use to order confirmatory tests for CKD?

- O – Do you feel like there is value in ordering confirmatory tests for CKD?
- O – Do you generally feel positive, negative or indifferent about ordering confirmatory tests for CKD?

- Ca – How easy or difficult is it for you to regularly order confirmatory tests for CKD?
- Ca – What problems have you encountered when ordering confirmatory tests for CKD? What would help resolve these problems?

- E/R – Are there resources or environmental factors that interfere or help with ordering confirmatory tests for CKD? What are these?
- E/R – Are there competing tasks and/ or time constraints? What are these?

- G – Do you feel that you should always order confirmatory tests for CKD?
- G – Are there other things you want to do for patients' care that might interfere with ordering these tests?

- M/A/D – Can you please describe what goes through your mind when deciding whether or not to order confirmatory tests for CKD?
- M/A/D – Might you decide not to order confirmatory tests for CKD – why or why not?

- RI – Is ordering confirmatory tests for CKD part of your professional role? Or do you think there's another health professional who should be doing this?
- RI – Is there anything in your professional role that would help you determine whether or not to order confirmatory tests for CKD (e.g., any protocols that you follow, other technologies)?

- R – Based on previous experiences with other patients, what encourages or discourages you to order confirmatory tests for CKD?

- Co – What do you think will happen if you do not order confirmatory tests for CKD?
- Co – Do you think the benefits of ordering these tests outweigh the costs (in terms of benefits and costs for you, your patients, etc.)?

- SI - How do others (i.e. colleagues, nurses, patients, etc.) influence your opinion on whether or not to order confirmatory tests for CKD? Do patient emotions or behaviours ever influence whether or not you order confirmatory tests for CKD?
- SI - Do your colleagues generally agree with you on your views and opinions for ordering confirmatory tests for CKD?

- E – Do your emotions ever influence your decision on whether or not to order confirmatory tests for CKD (for example, cognitive overload, stress)?

- BR – Have you developed any strategies or plans to help you order confirmatory tests for CKD?

Thank you, those are all the questions we have today. Is there anything else that you wanted to add on this topic that we did not discuss today?
We are trying to recruit other physicians for our study. Do you know other healthcare providers who might be interested in participating, if so, can you please provide their name(s) and contact information?

[Concluding interview]
Thank you so much for participating today and making an important contribution to our study. As a reminder, we will not be using your name or any other individual-level information in our reported findings. Please feel free to contact us if you have any questions or concerns about this study. If you are interested, we can send you an overview of the findings upon completion of this study in [insert number of months]. If so, can you please provide your email address [if I do not already have it]:

TDF Domain Key	
Knowledge	K
Skills	S
Social/ Professional Role Identity	RI
Beliefs about Capabilities	Ca
Optimism	O
Beliefs about Consequences	Co
Reinforcement	R
Intentions	I
Goals	G
Memory, Attention and Decision Processes	M/A/D
Environmental Context and Resources	E/R
Social Influences	SI

Emotion	E
Behavioural Regulation	BR

4. STUDY 3

Title: NSAID use and risk of acute kidney injury and hyperkalemia in older adults: a population-based study

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4.1 ABSTRACT

Background: Clinical guidelines caution against non-steroidal anti-inflammatory drugs (NSAID) use in older adults. The study objective was to quantify the 30-day risk of acute kidney injury and hyperkalemia in older adults after NSAID initiation, and to develop a model to predict these outcomes.

Methods: We conducted a population-based retrospective cohort study in Ontario, Canada from 2007 to 2015 of patients 66 years or older. We matched 46,107 new NSAID users to 46,107 non-users with similar baseline health. The primary outcome was 30-day risk of acute kidney injury, and secondary outcomes were hyperkalemia and all-cause mortality.

Results: NSAID use versus non-use was associated with a higher 30-day risk of acute kidney injury (380 (0.82%) versus 272 (0.59%), odds ratio 1.41, 95% confidence interval (CI) 1.20-1.65), and hyperkalemia (184 (0.40%) versus 123 (0.27%); odds ratio 1.50, 95% CI 1.20-1.89; risk difference 0.23%, 95% CI 0.13-0.34%). There was no association between NSAID use and all-cause mortality. A prediction model incorporated six predictors of acute kidney injury or hyperkalemia: older age, male gender, lower baseline estimated glomerular filtration rate, higher baseline serum potassium, angiotensin converting enzyme inhibitor or angiotensin receptor blocker use, or diuretic use. This model had moderate discrimination (c-statistic: 0.72, 95% CI 0.70-0.74) and good calibration. It is available as an online calculator.

Conclusions: In older adults, new NSAID use compared to non-use was associated with a higher 30-day risk of acute kidney injury and hyperkalemia. We developed a prediction model to estimate patients' risk of these events after NSAID prescription.

Abstract word count: 249

Keywords: Acute kidney injury, hyperkalemia, non-steroidal anti-inflammatory drugs, prediction model

4.2 INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used to treat pain and inflammation. Health Canada along with many clinical guidelines caution against NSAID use in older adults or patients with chronic kidney disease due to the risk of adverse events, including acute kidney injury (AKI) (Supplemental Table 1).(1–11) Over the last decade, 43% of older adults received at least one NSAID prescription in Ontario, Canada (Supplemental Methods 1). Furthermore, from 2006 to 2011, 16% of patients with chronic kidney disease in Ontario received at least one NSAID prescription for more than 14 days.(12) While there is evidence from a meta-analysis of case-control studies that NSAID use is associated with a higher risk of AKI,(13) studies that have assessed the risk of hyperkalemia have yielded conflicting results (Supplemental Table 2).(14–16) Therefore, we designed this large population-based cohort study to quantify the 30-day risk of AKI and hyperkalemia among older adults in Ontario, Canada who were dispensed more than a 14-day supply for NSAIDs, compared to older adults without prescription NSAID use. Because of the utility of risk-prediction tools for NSAID-induced gastrointestinal complications,(17–20) we also sought to develop and internally validate a prediction model to quantify a patient's 30-day risk of developing AKI or hyperkalemia after NSAID initiation based on patient characteristics at the time of prescribing.

4.3 MATERIALS AND METHODS

Study Design and Research Setting

Ontario has more than 13 million residents, 17% of whom are 65 years or older.(21) Healthcare services in Ontario are publically funded; with the exception of outpatient medications, which are only funded for individuals aged 65 years and older, and other special populations.(22) These healthcare encounters are recorded in administrative databases held ICES. All databases are linked using unique, encoded identifiers.

We conducted a population-based, retrospective cohort study using healthcare data at ICES. The use of ICES data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require Research Ethics Board review. We followed reporting guidelines for observational and prediction studies (Supplemental Tables 3 & 4).(23,24)

Data Sources

We used the Ontario Drug Benefit database to identify prescriptions for individuals aged 65 and older. This database contains accurate records of all dispensed outpatient prescriptions.(25) We used the Ontario Laboratories Information System database to identify laboratory values and estimated glomerular filtration rates (eGFR) using the Chronic Kidney Disease Epidemiology (CKD-EPI) equation.(26) We had no information on race and assumed all patients to be non-black for the CKD-EPI equation (less than 5% of the Ontario population is of black race).(27) We used seven additional linked databases held at ICES to ascertain information on hospitalizations and emergency department visits (Canadian Institute for Health Information's Discharge Abstract Database and National Ambulatory Care Reporting System), physician billings (Ontario Health

Insurance Plan database), prescribing physicians (ICES Physician database, Client Agency Program Enrolment), treatment for end-stage kidney disease (the Ontario portion of the Canadian Organ Replacement Register), and demographics (Registered Persons Database).

We used the 10th edition of the Canadian Modified International Classification of Disease system to define comorbidities and the Canadian Classification for Health Interventions to define healthcare procedures. We also used the Johns Hopkins' Aggregated Diagnosis Groups and the Expanded Diagnosis Clusters to assess baseline comorbidity (Johns Hopkins' ACG® System Version 10.0).(28)

Our data sources were complete for all study variables except for NSAID prescriber data (15% missing), rural status (<0.005% missing), and income quintile (<0.5% missing). Emigration from Ontario is very low (0.1% per year) and was the only reason for lost study follow-up.(29)

Cohort Assembly and Exposure Categorization

We identified geographic areas across time where residents would likely visit a hospital with linked laboratory data (referred to as the laboratory catchment area). We included Ontarians who resided within this catchment area between April 1, 2007 and September 30, 2015. In the exposed group, we identified patients with an NSAID prescription filled between April 1, 2007 and August 31, 2015 with more than a 14-day supply. For patients with multiple eligible NSAID prescriptions after exclusions, we restricted to the first one. See Supplemental Table 5 for list of eligible drug names. The date of NSAID dispensing

was referred to as the index date, also called the cohort entry date. For patients in our comparison group without an NSAID prescription, we randomly assigned an index date based on the distribution of index dates in the NSAID user group.

We excluded the following patients: 1) those in their first year of provincial drug coverage (between age 65 and 66) to avoid incomplete medication history, 2) those with an NSAID prescription in the prior six months to ensure new users only, 3) those discharged from hospital in the two days prior to index date to ensure new outpatient prescriptions, since patients who initiate treatment in hospital fill ongoing prescriptions on the hospital discharge date or the day after, 4) those without at least one outpatient value for both serum creatinine and serum potassium in the prior year to assess baseline kidney function and potassium levels, 5) those with baseline serum potassium values greater than 5.5 mEq/L (5.5 mmol/L) or potassium binder prescriptions in the past six months, 6) those with a baseline eGFR greater than 150 mL/min/1.73 m^2, which was likely a data error, 7) those not in the laboratory catchment area on their index date to reliably assess laboratory results in follow-up, and 8) patients with end-stage kidney disease, as an outcome of AKI is not relevant. For patients in the non-user group, we excluded anyone without at least one healthcare encounter in our physician claims or drug benefit databases in the past 30 days to ensure that patients were accessing the Ontario healthcare system.

Outcomes

Our primary outcome was AKI, defined by the 2012 Kidney Disease Improving Global Outcomes (KDIGO) thresholds: compared to baseline, a serum creatinine increase of 50% or more, or an absolute increase of at least 0.3 mg/dL (26.5 μmol/L).(30) We selected an outpatient serum creatinine value within the past year that was closest to the index date. We compared this baseline value to the highest serum creatinine value in the following 30 days, whether the measurement was done in the community, emergency department or during a hospitalization. In additional analyses, we assessed more severe AKI, defined according to KDIGO staging thresholds (Supplemental Table 6).(30) We assessed all outcomes in the 30 days following the index date, since AKI onset generally occurs within two weeks of NSAID initiation.(31)

Our secondary outcomes were hyperkalemia, all-cause mortality, and a composite of AKI or hyperkalemia. We defined hyperkalemia as a serum potassium value in an outpatient, emergency department, or inpatient setting that was 5.5 mEq/L or greater. In additional analyses, we assessed outcomes of more severe hyperkalemia defined as values of 6.0 and 6.5 mEq/L or greater.

Statistical Analyses

We conducted all analyses using SAS version 9.4 (SAS Institute, Cary, NC). We compared baseline characteristics between NSAID users and non-users using standardized mean differences, where a difference of 10% or more was considered significant.(32) We calculated a propensity score for the probability of receiving an NSAID prescription using a multivariable logistic regression model that incorporated

more than 150 baseline characteristics (including indications for NSAID use and risk factors for AKI and hyperkalemia; Supplemental Table 7). We matched NSAID users to non-users 1:1 using greedy matching without replacement.(33) Matching criteria included eGFR (±5 mL/min/1.73 m^2), serum potassium (±0.5 mmol/L), angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) use, diuretic use (categorized as 1) potassium-sparing, or 2) loop or thiazide), and the logit of the propensity score (±0.2 standard deviations).

We performed conditional logistic regression analyses to estimate odds ratios and 95% confidence intervals (CI). Given the low incidences observed, we approximated all odds ratios as relative risks. We estimated the risk difference between the groups, and the number needed to harm.(34) This latter measure indicates how many patients need to receive an NSAID prescription for one patient to have an adverse event who would not have experienced this event in the absence of an NSAID prescription. For AKI, we performed sub-group analyses on baseline eGFR, ACEi / ARB use, diuretic use, and NSAID dose measured as the percentage of the maximum daily dose (for this sub-group non-users followed their matched users). For hyperkalemia, we performed the same sub-group analyses with the addition of baseline serum potassium. We performed an additional analysis for the primary AKI outcome where we restricted the analysis to patients who received at least one serum creatinine test within the 30-day follow-up. We did not account for matching in this additional analysis, since the matched pairs were separated. We interpreted two-tailed $P<0.05$ as statistically significant in all analyses.

We developed a prediction model of 30-day AKI or hyperkalemia risk among all NSAID users and followed relevant reporting guidelines (Supplemental Table 4).(24) For the potential predictors, we identified the following variables *a priori* that are easily ascertained in practice and were associated with higher risk of AKI or hyperkalemia in the literature: higher age,(35–37) female sex,(36,38) lower baseline eGFR,(35,36,38) higher baseline serum potassium concentration,(39) higher NSAID dose,(40,41) ACEi / ARB use,(35,42) and use of loop, potassium-sparing, or thiazide-type diuretics.(35,37,42) We kept continuous variables continuous and assumed that their relationship with the outcome was linear.

We performed stepwise multivariable logistic regression using a $P<0.05$ threshold to retain variables. We assessed model discrimination using the c-statistic, which describes the ability of our model to assign higher predicted risks to those with the outcome versus those without.(43) We assessed model calibration by plotting the predicted probabilities versus the observed risk of the outcome using locally weighted scatterplot smoothing (LOESS).(44) We validated the model internally using 200 bootstrap samples selected with replacement from the NSAID users.(45) We repeated stepwise logistic regression for each of these 200 samples and used Harrell's optimism for the C-statistic to estimate how the model might perform in new data.(45) Finally, we created an online calculator for ease of use.

4.4 RESULTS

See Figure 1 for cohort assembly. We identified 9,131,660 individuals in the laboratory catchment area, where 428,825 received at least one NSAID prescription for greater than 14 days. After exclusions, we had 61,219 NSAID users and 156,589 non-users. We matched 46,107 NSAID users to 46,107 non-users, and matched pairs were similar across over 150 baseline characteristics (see Table 1 for select baseline characteristics and Supplemental Table 7 for full baseline table). The mean age was 74 years and 58% were women.

Primary Outcome: Acute Kidney Injury

NSAID use was associated with a higher 30-day risk of AKI: 380 (0.82%) versus 272 (0.59%) events, respectively; OR, 1.41 (95% CI, 1.20-1.65); risk difference, 0.23% (95% CI, 0.13-0.34%). This association was consistent across AKI stages (Table 2). Baseline eGFR, ACEi or ARB use, diuretic use, and NSAID dose did not significantly modify the association between NSAID use and AKI (Figure 2).

Secondary Outcomes: Hyperkalemia and All-Cause Mortality

NSAID use was associated with a higher 30-day risk of hyperkalemia: 184 (0.40%) versus 123 (0.27%) events, respectively; OR, 1.50 (95% CI, 1.20-1.89). We did not observe a statistically significant association between NSAID use and higher thresholds of hyperkalemia (serum potassium ≥6.0 or ≥6.5 mEq/L); there were few events and estimates were imprecise (Table 2). Baseline serum potassium, eGFR, ACEi or ARB use,

diuretic use, and NSAID dose did not significantly modify the association between NSAID use and hyperkalemia (Supplemental Figure 1).

NSAID use was associated with a higher 30-day risk of AKI or hyperkalemia: 510 (1.11%) versus 370 (0.80%) events, respectively; OR, 1.39 (95% CI, 1.21-1.59). NSAID use versus non-use was not significantly associated with all-cause mortality: 66 (0.14%) versus 79 (0.17%) events, respectively; OR, 0.83 (95% CI, 0.60-1.16).

Additional Analysis

Over 30-day follow-up, 16% (15,030) and 14% (12,519) of patients had at least one serum creatinine and serum potassium test completed, respectively. Among those with a follow-up serum creatinine test, 17% (7804) were NSAID users and 16% (7226) were non-users. We found similar risk estimates when we looked at the association between NSAID use and AKI only among the 15,030 people with follow-up serum creatinine tests (Table 2).

Prediction Model

Among 61,219 NSAID users, 701 (1.15%) developed AKI or hyperkalemia in the 30 days following prescription. Our model included six predictors of AKI or hyperkalemia: older age, male gender, lower baseline eGFR, higher baseline serum potassium, ACEi or ARB prescription, and diuretic prescription (Supplemental Table 8).

Predicted risk ranged from 0.05% to 22.6%. The optimism-adjusted c-statistic was 0.72 (95% CI, 0.70-0.74), indicating moderate discrimination (Supplemental Figure 2), and the model had good calibration (Figure 3). Supplemental Table 9 demonstrates the clinical utility of the model to identify high-risk patients based on predicted risk thresholds of >1%, >5% and >10%. The sensitivity ranged from 2.6% to 67.8% and the specificity from 64.1% to 99.8%. This model is available as an online calculator: [available_at_time_of_publication].

4.5 DISCUSSION

In this large population-based cohort study of older adults, we found that receiving a new NSAID prescription (with a day supply greater than 14 days) was associated with a higher 30-day risk of AKI and hyperkalemia compared to no prescription NSAID use. However, absolute 30-day risks of AKI and hyperkalemia after NSAID initiation were low (<1%). We also found that NSAID users did not have a higher risk of 30-day mortality. This was likely because the majority of the adverse outcomes were mild: 79% of AKI events were stage one and 63% of people with hyperkalemia had serum potassium values from 5.5 to 6 mEq/L.

A systematic review and meta-analysis by Zhang et al. (2017), examining 1.6 million people from 10 case-control studies, showed NSAID use versus non-use was associated with a 70% greater odds of developing AKI.(13) Similarly, we found a 40% greater relative risk of AKI with NSAID use compared to non-use. A recent population-based retrospective cohort study from Ontario, Canada of older patients with chronic

kidney disease, congestive heart failure or hypertension found a new NSAID prescription compared to no such prescription was not associated with a higher risk of hospitalization with AKI, hospitalization with hyperkalemia, or death within 30 days of prescription date.(46) However, these authors used diagnosis codes to define hospitalization with AKI and hyperkalemia, which are known to have low sensitivity compared to laboratory data.(47,48)

The association between NSAID use and hyperkalemia is less consistent in the literature. Two large case-control studies comparing NSAID use versus no use found opposing results.(14,16) Our large population-based cohort study helps remove some of the uncertainty of hyperkalemia risk, since we found that NSAID use was associated with a 50% increased risk of developing hyperkalemia.

Clinical guidelines recommend that patients with chronic kidney disease avoid NSAIDs.(2–6) In our study, baseline eGFR did not significantly modify the relative association between NSAID use and AKI risk. Consistent with our findings, Zhang et al. (2017) also found that patients with chronic kidney disease had a similar relative risk of AKI with NSAID use compared to the general population.(13) However, patients with lower baseline eGFR have the highest absolute increase in AKI risk with NSAID use.

We developed a prediction model that may be useful to discriminate between people at low versus high risk of AKI or hyperkalemia if they initiated NSAID treatment. Our model predicted patients' risk of experiencing AKI or hyperkalemia within 30 days of NSAID initiation with acceptable accuracy. Using a predicted risk threshold of more than 5%, we showed that our model had high specificity, which means we can be

confident that people with a predicted risk above 5% are truly at high risk. Using our model, clinicians can identify high-risk patients who should either receive serum creatinine and potassium monitoring after initiating NSAIDs, or avoid taking NSAIDs altogether. This model should be externally validated in other datasets and populations.

Study Strengths and Limitations

We completed a large population-based study to assess the association of an uncommon, yet important complication of NSAID use among older adults. This is the first study to use a cohort design with laboratory data to quantify the absolute risk of AKI and hyperkalemia with NSAID use. This is also the first study to develop a prediction model to estimate patients' risk of developing these outcomes after NSAID prescription. Given the observational study design, we cannot infer causality. Although we cannot completely eliminate residual confounding, we attempted to reduce it by using propensity scores to balance patients on over 150 baseline characteristics.

We used laboratory data to ascertain AKI and hyperkalemia events because these events are underrepresented in administrative databases.(47,48) This also allowed us to examine associations among subgroups with varying baseline risk of our outcomes, as everyone required a baseline serum creatinine and potassium value. However, we only captured patients who received laboratory tests as part of routine care (~15% of cohort). There may have been a tendency for NSAID users to receive testing compared to non-users (17% versus 16%); however, we do not expect this small difference to bias our results, since we showed a similar association between NSAID use and AKI in the

additional analysis when only including patients who had a follow-up serum creatinine test.

Another limitation is that we only had data on NSAID prescriptions, and are unaware of over-the-counter NSAID use. However, researchers have shown that not accounting for over-the-counter medications likely contributes only a small amount of bias.(49) Another limitation is that we could only identify prescriptions dispensed by a pharmacy, and we do not know if patients were taking their medications. Similarly, patients may take NSAIDs on an as-needed basis rather than daily. Both these limitations – the possibility of the non-user group taking over-the-counter NSAIDs and the NSAID users not taking their medication as prescribed – would likely attenuate the estimated effect of NSAID use on AKI and hyperkalemia.

We only included patients older than 66 years, but our findings were consistent with other studies that have included adults of all ages.(14,16)

Conclusions

In summary, we found that older adults prescribed NSAIDs for more than 14 days are at greater risk for AKI and hyperkalemia in the following 30 days compared to similar patients not prescribed NSAIDs; however, this did not translate into an increased short-term mortality risk. Therefore, prescription NSAID use among many older adults may be safe, but providers should still use caution and assess individual patient risk. Our prediction model can help to inform clinical decision making for NSAID prescribing and laboratory monitoring in an older population.

Conflict of interest statement: All authors declare no conflicts of interest.

Authors' contributions: DMN and AXG developed the initial study and analysis plan. KSB, MMR, EM, JCF, PR, and MAW provided input and approved of the study and analysis plan. DMN completed all data programming and statistical analyses. All authors helped with interpretation of the results. PR created the online calculator. DMN drafted the initial manuscript with oversight by AXG, and all other authors critically reviewed and revised the manuscript. All authors reviewed and approved the final manuscript.

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4.7 TABLES & FIGURES

Table 1. Select baseline characteristics of the cohort before and after matching

Variable	Baselines Pre-Match			Baselines Post-Match		
	NSAID users n=61,219	Non-users n=156,589	Stan. Diff.	NSAID users n=46,107	Non-users n=46,107	Stan. Diff.
Demographics						
Age, mean (SD), year	74.1 (6.4)	76.0 (8.1)	27%	74.2 (6.5)	74.2 (7.1)	1%
Female sex, No. (%)	36,016 (58.8)	84,355 (53.9)	10%	26,654 (57.8)	26,552 (57.6)	0%
Rural status, No. (%)[a]	3,489 (5.7)	8,431 (5.4)	1%	2,298 (5.0)	2,334 (5.1)	0%
Income quintile, No. (%)[b]						
1 (lowest)	11,523 (18.8)	26,116 (16.7)	5%	8,337 (18.1)	8,234 (17.9)	1%
2	12,365 (20.2)	29,469 (18.8)	4%	9,215 (20.0)	9,055 (19.6)	1%
3	12,823 (20.9)	31,049 (19.8)	3%	9,510 (20.6)	9,457 (20.5)	0%
4	12,653 (20.7)	33,721 (21.5)	2%	9,622 (20.9)	9,680 (21.0)	0%
5 (highest)	11,855 (19.4)	36,234 (23.1)	9%	9,423 (20.4)	9,681 (21.0)	1%
Index prescription information						
Index NSAID is a COX2 inhibitor, No. (%)	30,741 (50.2)			23,208 (50.3)		
Percentage of maximum daily dosage, mean (SD)	61.9 (28.3)			61.5 (28.2)		
Prescribing physician characteristics						
Age, mean (SD), year	55.6 (11.3)			55.8 (11.3)		
Missing, No. (%)	3,256 (5.3)			2,395 (5.2)		
Female sex, No. (%)	15,972 (26.1)			12,019 (26.1)		
Missing, No. (%)	2,620 (4.3)			1,862 (4.0)		
Rural status, No. (%)	2,719 (4.4)			1,778 (3.9)		
Missing, No. (%)	2,574 (4.2)			1,827 (4.0)		
Medical specialty, No. (%)						
Primary care	52,772 (86.2)			40,040 (86.8)		
Nephrologist	54 (0.1)			38 (0.1)		
Cardiologist	127 (0.2)			107 (0.2)		
Other	5,694 (9.3)			4,097 (8.9)		
Missing	2,572 (4.2)			1,825 (4.0)		
Number of healthcare visits in prior year						
Hospitalizations, mean (SD)	0.2 (0.5)	0.2 (0.6)	11%	0.1 (0.5)	0.1 (0.5)	0%
Emergency	0.5 (1.2)	0.5 (1.1)	3%	0.5 (1.2)	0.5 (1.1)	1%

Variable	Baselines Pre-Match			Baselines Post-Match		
	NSAID users n=61,219	Non-users n=156,589	Stan. Diff.	NSAID users n=46,107	Non-users n=46,107	Stan. Diff.
department, mean (SD)						
Family physician, mean (SD)	9.2 (7.4)	8.9 (9.4)	4%	8.8 (7.2)	8.7 (8.0)	2%
Nephrologist, mean (SD)	0.1 (0.6)	0.2 (1.0)	15%	0.1 (0.6)	0.1 (0.5)	0%
Comorbidity in past 5 years, No. (%)						
Charlson comorbidity score						
0 or no hospitalization	46,909 (76.6)	104,469 (66.7)	22%	35,055 (76.0)	34,918 (75.7)	1%
1	6,668 (10.9)	19,989 (12.8)	6%	5,017 (10.9)	5,089 (11.0)	0%
2	4,426 (7.2)	15,417 (9.8)	9%	3,442 (7.5)	3,493 (7.6)	0%
3 or more	3,216 (5.3)	16,714 (10.7)	20%	2,593 (5.6)	2,607 (5.7)	0%
John Hopkins ADG Score, mean (SD)	12.4 (4.0)	11.6 (4.2)	18%	12.1 (4.0)	12.1 (4.0)	1%
Ischemic heart disease	15,950 (26.1)	49,501 (31.6)	12%	12,150 (26.4)	12,265 (26.6)	0%
Congestive heart failure	4,105 (6.7)	21,268 (13.6)	23%	3,178 (6.9)	3,269 (7.1)	1%
Ventricular arrhythmia	91 (0.1)	791 (0.5)	7%	71 (0.2)	76 (0.2)	0%
Myocardial infarction	2,119 (3.5)	8,828 (5.6)	10%	1,634 (3.5)	1,686 (3.7)	1%
Peripheral vascular disease	2,320 (3.8)	7,572 (4.8)	5%	1,752 (3.8)	1,736 (3.8)	0%
Atrial fibrillation	1,548 (2.5)	12,489 (8.0)	25%	1,277 (2.8)	1,407 (3.1)	2%
Coronary artery bypass graft	570 (0.9)	2,301 (1.5)	6%	450 (1.0)	479 (1.0)	0%
Percutaneous coronary intervention	1,360 (2.2)	4,957 (3.2)	6%	1,091 (2.4)	1,093 (2.4)	0%
Diabetes	22,177 (36.2)	57,397 (36.7)	1%	16,653 (36.1)	16,610 (36.0)	0%
Hypertension	46,410 (75.8)	116,542 (74.4)	3%	34,526 (74.9)	34,391 (74.6)	1%
Chronic liver disease	642 (1.0)	2,455 (1.6)	5%	509 (1.1)	519 (1.1)	0%
Chronic lung disease	14,709 (24.0)	34,723 (22.2)	4%	10,473 (22.7)	10,403 (22.6)	0%
Malignancy	7,407 (12.1)	21,501 (13.7)	5%	5,669 (12.3)	5,657 (12.3)	0%
Osteoporosis	10,193 (16.7)	23,428 (15.0)	5%	7,570 (16.4)	7,519 (16.3)	0%
Joint disease	34,669 (56.6)	44,363 (28.3)	60%	23,064 (50.0)	22,681 (49.2)	2%
Joint disorder	7,378 (12.1)	9,779 (6.2)	21%	4,706 (10.2)	4,572 (9.9)	1%
Bursitis	18,345 (30.0)	23,268 (14.9)	37%	11,902 (25.8)	11,626 (25.2)	1%
Fibromyalgia	4,417 (7.2)	5,305 (3.4)	17%	2,686 (5.8)	2,514 (5.5)	1%
Fracture	7,630 (12.5)	20,413 (13.0)	1%	5,634 (12.2)	5,558 (12.1)	0%
Hip fracture	531 (0.9)	3,297 (2.1)	10%	436 (0.9)	454 (1.0)	1%
Back pain	30,486 (49.8)	41,164 (26.3)	50%	20,383 (44.2)	20,051 (43.5)	1%
Back surgery	790 (1.3)	836 (0.5)	8%	454 (1.0)	428 (0.9)	1%

Variable	Baselines Pre-Match			Baselines Post-Match		
	NSAID users n=61,219	Non-users n=156,589	Stan. Diff.	NSAID users n=46,107	Non-users n=46,107	Stan. Diff.
Knee surgery	3,829 (6.3)	3,755 (2.4)	19%	2,221 (4.8)	2,130 (4.6)	1%
Hip surgery	1,612 (2.6)	2,604 (1.7)	6%	1,091 (2.4)	1,091 (2.4)	0%
Cerebrovascular disease	4,783 (7.8)	20,211 (12.9)	17%	3,765 (8.2)	3,778 (8.2)	0%
Dementia	3,729 (6.1)	24,123 (15.4)	30%	3,142 (6.8)	3,106 (6.7)	0%
Migraine	2,649 (4.3)	4,491 (2.9)	8%	1,801 (3.9)	1,804 (3.9)	0%
Gout	4,985 (8.1)	4,581 (2.9)	23%	2,804 (6.1)	2,426 (5.3)	3%
Rheumatoid arthritis	3,994 (6.5)	4,517 (2.9)	17%	2,436 (5.3)	2,320 (5.0)	1%
Osteoarthritis	7,031 (11.5)	7,861 (5.0)	24%	4,245 (9.2)	4,163 (9.0)	1%
Sciatica	21,449 (35.0)	26,131 (16.7)	43%	13,872 (30.1)	13,479 (29.2)	2%
Pain	32,285 (52.7)	54,717 (34.9)	36%	22,548 (48.9)	22,434 (48.7)	0%
Schizophrenia	704 (1.1)	3,766 (2.4)	10%	576 (1.2)	580 (1.3)	1%
Depression	5,161 (8.4)	13,267 (8.5)	0%	3,729 (8.1)	3,766 (8.2)	0%
Healthcare procedures in prior year, No. (%)						
Carotid ultrasound	2,812 (4.6)	8,492 (5.4)	4%	2,179 (4.7)	2,230 (4.8)	0%
Coronary angiogram	1,005 (1.6)	3,557 (2.3)	5%	785 (1.7)	797 (1.7)	0%
Coronary revascularization	415 (0.7)	1,731 (1.1)	4%	344 (0.7)	359 (0.8)	1%
Echocardiogram	12,466 (20.4)	37,234 (23.8)	8%	9,526 (20.7)	9,649 (20.9)	0%
Holter test	4,684 (7.7)	14,820 (9.5)	6%	3,616 (7.8)	3,675 (8.0)	1%
Stress test	8,472 (13.8)	19,822 (12.7)	3%	6,223 (13.5)	6,213 (13.5)	0%
Cardiac catheterization	1,032 (1.7)	3,699 (2.4)	5%	807 (1.8)	819 (1.8)	0%
Back x-ray	29,048 (47.4)	44,677 (28.5)	40%	19,685 (42.7)	19,347 (42.0)	1%
At least one albumin-to-creatinine test	35,803 (58.5)	79,468 (50.7)	16%	26,481 (57.4)	26,330 (57.1)	1%
Laboratory tests in prior year						
Time from baseline serum creatinine to index date, median (IQR), days	94 (33-192)	88 (34-179)		94 (32-193)	95 (37-187)	
Baseline serum creatinine value, mean (SD), mg/dL	0.9 (0.3)	1.0 (0.4)	27%	0.9 (0.3)	0.9 (0.3)	0%
Baseline eGFR value, mean (SD), mL/min/1.73 m^2	73.0 (16.0)	69.1 (18.6)	23%	73.0 (16.0)	73.0 (16.0)	0%
Baseline potassium value, mean (SD), mEq/L	4.4 (0.4)	4.4 (0.4)	2%	4.4 (0.4)	4.4 (0.4)	0%
Prescriptions in prior 120 days, No. (%)						
Aspirin	1,549 (2.5)	2,532 (1.6)	6%	1,018 (2.2)	959 (2.1)	1%
Tylenol	2,939 (4.8)	2,879 (1.8)	17%	1,664 (3.6)	1,473 (3.2)	2%
Opiates	12,499 (20.4)	15,521 (9.9)	30%	7,697 (16.7)	7,166 (15.5)	3%
Angiotensin converting enzyme	15,898 (26.0)	48,917 (31.2)	12%	12,190 (26.4)	12,190 (26.4)	0%

Variable	Baselines Pre-Match			Baselines Post-Match		
	NSAID users n=61,219	Non-users n=156,589	Stan. Diff.	NSAID users n=46,107	Non-users n=46,107	Stan. Diff.
inhibitor						
Angiotensin receptor blocker	16,618 (27.1)	37,556 (24.0)	7%	12,139 (26.3)	12,139 (26.3)	0%
Statin	32,296 (52.8)	84,994 (54.3)	3%	24,343 (52.8)	24,269 (52.6)	0%
Diabetes drug	13,159 (21.5)	37,247 (23.8)	5%	10,097 (21.9)	10,087 (21.9)	0%
Calcium channel blocker	16,386 (26.8)	45,357 (29.0)	5%	12,400 (26.9)	12,244 (26.6)	1%
Beta-blocker	14,136 (23.1)	48,987 (31.3)	19%	10,921 (23.7)	11,045 (24.0)	1%
Proton pump inhibitor	24,196 (39.5)	40,148 (25.6)	30%	16,246 (35.2)	15,737 (34.1)	2%
Thiazide diuretic	8,871 (14.5)	22,768 (14.5)	0%	6,461 (14.0)	6,466 (14.0)	0%
Loop diuretic	3,137 (5.1)	16,247 (10.4)	20%	2,270 (4.9)	2,213 (4.8)	0%
Potassium-sparing diuretic	1,877 (3.1)	6,000 (3.8)	4%	1,251 (2.7)	1,230 (2.7)	0%

Abbreviations: ADG, Aggregated Diagnostic Group; eGFR, estimated glomerular filtration rate; IQR, interquartile range; NSAIDs, non-steroidal anti-inflammatory drugs; Stan. Diff., standardized difference; SD, standard deviation.

SI conversion factors: To convert serum creatinine from mg/dL to μmol/L, multiply by 88.4; to convert serum potassium from mEq/L to mmol/L multiply by 1.0.

[a]Missing rural status was categorized as not rural

[b]Missing income quintile was imputed into the third quintile

Table 2. 30-day primary and secondary outcomes of prescription NSAID users compared to non-users

Outcome	NSAID users, number of events (%) n=46,107	Non-users, number of events (%) n=46,107	Odds Ratio (95% CI)	Risk Difference (95% CI)	Number Needed to Harm (95% CI)
AKI[a]	380 (0.82)	272 (0.59)	1.41 (1.20-1.65)	0.23 (0.13-0.34)	427 (292-787)
AKI stage 2 or more[b]	60 (0.13)	40 (0.09)	1.50 (1.01-2.24)	0.04 (0.00-0.09)	2305 (1164-114,916)
AKI stage 3[c]	25 (0.05)	12 (0.03)	2.08 (1.05-4.15)	0.03 (0.002-0.05)	3547 (1848-43,478)
Hyperkalemia (≥5.5 mEq/L)	184 (0.40)	123 (0.27)	1.50 (1.20-1.89)	0.13 (0.06-0.2)	756 (485-1715)
Hyperkalemia (≥6.0 mEq/L)	38 (0.08)	30 (0.07)	1.27 (0.79-2.04)	0.02 (-0.02-0.05)	N/A
Hyperkalemia (≥6.5 mEq/L)	16 (0.03)	30 (0.02)	2.29 (0.94-5.56)	0.02 (0.00-0.04)	N/A
Composite of AKI[a] or hyperkalemia (≥5.5 mEq/L)	510 (1.11)	370 (0.80)	1.39 (1.21-1.59)	0.30 (0.18-0.43)	329 (234-558)
All-cause mortality	66 (0.14)	79 (0.17)	0.83 (0.60-1.16)	-0.03 (-0.08-0.02)	N/A
AKI additional analysis[a,d]	380 (4.87)	272 (3.76)	1.31 (1.12-1.53)	1.11 (0.46-1.75)	90 (57-217)

Abbreviations: AKI, acute kidney injury; CI, confidence interval; N/A, not applicable; NSAIDs, non-steroidal anti-inflammatory drugs.

SI conversion factor: To convert serum potassium from mEq/L to mmol/L multiply by 1.0.

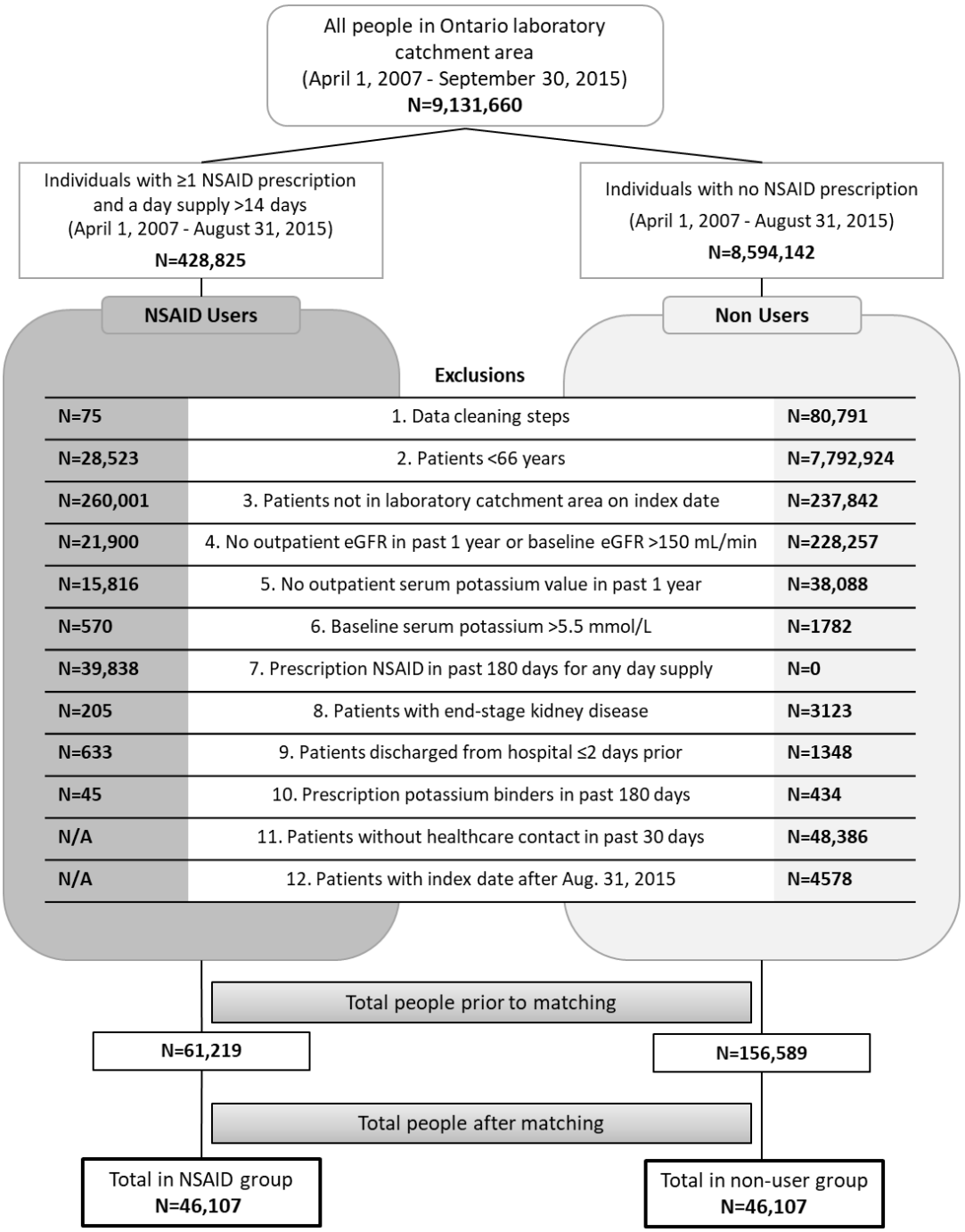
[a]The primary definition of AKI was a serum creatinine increase of 50% or more or an absolute increase of at least 0.3 mg/dL (26.5 µmol/L) compared to baseline.

[b]A serum creatinine increase of 100% but less than 200% from baseline.

[c]A serum creatinine increase of at least 200% from baseline, an absolute value of 4.0 mg/dL (353.6 µmol/L), or receipt of acute dialysis.

[d]Analysis performed among 15,030 people with 30-day follow-up serum creatinine tests (7804 NSAID users and 7226 non-users).

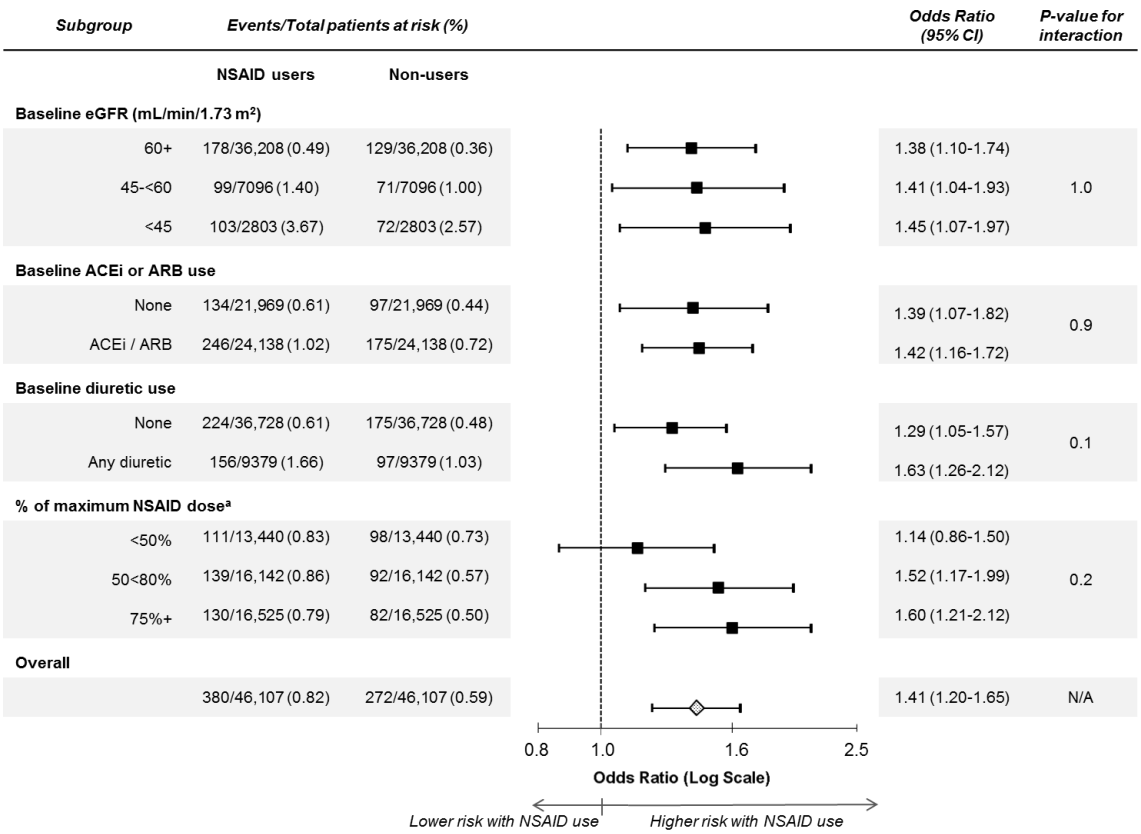
Figure 1. Cohort assembly for patients in the NSAID user group and the matched non-user group



Abbreviations: eGFR, estimated glomerular filtration rate; N/A, not applicable; NSAIDs, non-steroidal anti-inflammatory drugs.

Note: exclusions 11 and 12 were only applied to non-user group.

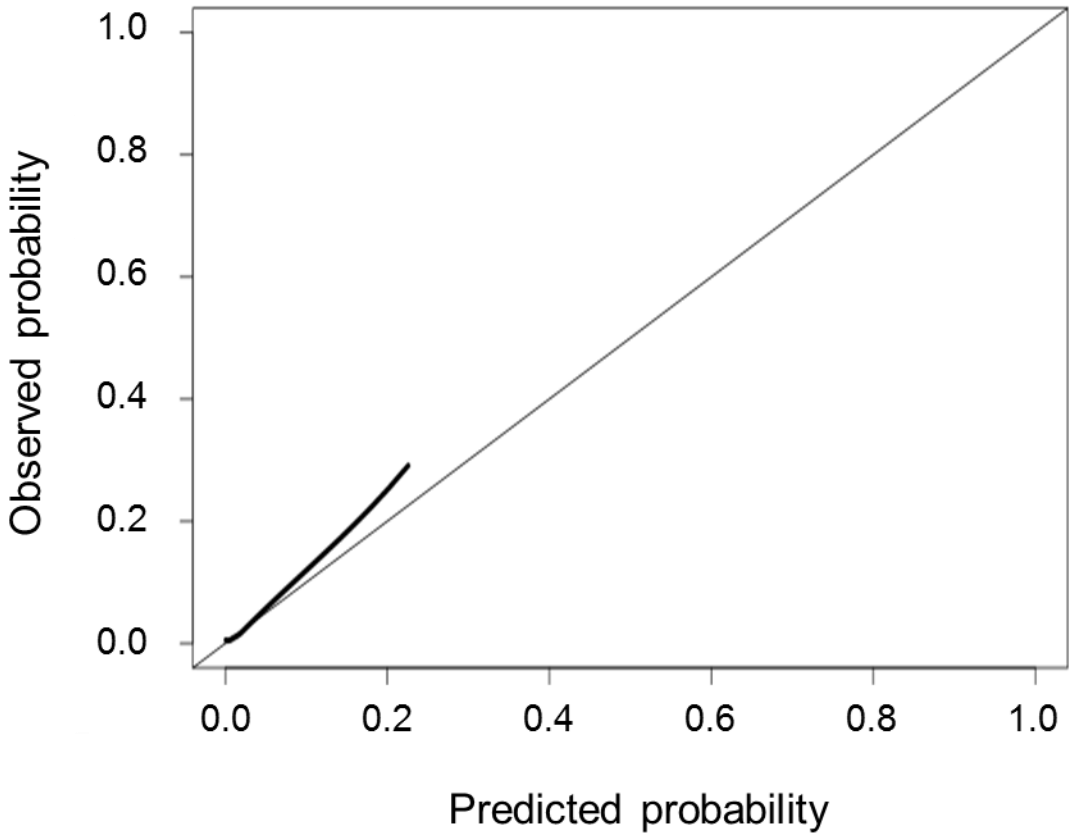
Figure 2. Sub-group analyses for the outcome of acute kidney injury from prescription NSAID use



Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; eGFR, estimated glomerular filtration rate; N/A, not applicable; NSAIDs, non-steroidal anti-inflammatory drugs.

[a]We defined % of maximum NSAID daily dose by the NSAID group, with the non-user group following their matched NSAID user.

Figure 3. Calibration plot of predicted probabilities versus observed events of acute kidney injury or hyperkalemia among patients in the NSAID user group



4.8 SUPPLEMENTAL MATERIAL

Title: NSAID use and risk of acute kidney injury and hyperkalemia in older adults: a population-based study

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Supplemental Table 1. Clinical guidelines for recommendations against prescribing NSAIDs in certain patient groups

Disease/ condition	Guideline	Recommendation	Strength & Quality of Recommendation
Chronic kidney disease	KDIGO 2013(1)	"We recommend temporary discontinuation of potentially nephrotoxic and renally excreted drugs in people with a GFR <60 ml/min/1.73 m2 (GFR categories G3a-G5) who have serious intercurrent illness that increases the risk of AKI. These agents include… NSAIDs..."	1C – we recommend; low evidence.
Chronic kidney disease	KDOQI 2002(2)	"The avoidance of potential nephrotoxins, such as intravenous radiographic contrast, certain antibiotics, and NSAIDs must be based on an individualized assessment of the risks of acute decline in GFR versus the therapeutic benefits of treatment."	R – review of reviews and selected original articles
Hypertension	Hypertension Canada CHEP Guidelines 2016(3)	"Exogenous factors that can induce or aggravate hypertension should be assessed and removed if possible… Examples of exogenous factors that can induce/ aggravate hypertension: NSAIDs."	N/A
Hypertension	American Society of Hypertension and the International Society of Hypertension (2013)(4)	"Ask about concurrent drugs. Commonly used drugs (for indications unrelated to treating hypertension) can increase blood pressure and therefore should be stopped if possible. These include nonsteroidal anti-inflammatory drugs used for arthritis and pain relief…"	N/A
Diabetes	Canadian Diabetes Association: Canadian Journal of Diabetes (2013)(5)	"Nonsteroidal anti-inflammatory drugs cause constriction of the afferent arterioles, which can further reduce blood flow into the glomerulus in patients who are volume contracted. For these reasons, all of these drugs can reduce kidney function during times of intercurrent illness. Consideration should be given to providing patients with a "sick day" medication list, instructing the patient to hold these medications if they feel that they are becoming dehydrated for any reason…"	N/A
Heart Failure	ACCF/ AHA Guideline for	"Drugs known to adversely affect the clinical status of patients with current	Level B (limited populations evaluated)

Disease/ condition	Guideline	Recommendation	Strength & Quality of Recommendation
	the Management of Heart Failure 2013(6)	or prior symptoms of [heart failure with reduced ejection fraction] are potentially harmful and should be avoided or withdrawn whenever possible (e.g… NSAIDs…)"	
Geriatrics and Pain	American Geriatrics Society Panel(7)	"Nonselective NSAIDs and COX-2 selective inhibitors may be considered rarely, and with extreme caution, in highly selected individuals (high quality of evidence, strong recommendation)." "Absolute contraindications: …chronic kidney disease (moderate level of evidence, strong recommendation), heart failure (moderate level of evidence, weak recommendation)."	See recommendation.
NSAID drug therapy	Canadian Consensus Guidelines on long-term NSAID drug therapy(8)	Traditional NSAIDs and COX-2 selective inhibitors increase risk of hypertension, kidney impairment and fluid retention.	Grade B (moderate quality evidence)
NSAID drug therapy	Health Canada 2006(9)	Patients should not take NSAIDs if they have severe kidney disease or steadily declining kidney function. NSAIDs should be taken with caution when patients have pre-existing kidney disease.	N/A
Chronic kidney disease	National Kidney Foundation: Position paper on analgesics and the kidney 1996(10)	There should be a warning on the labels of over-the-counter NSAIDs informing patients that they should not take the medication without physician supervision if they have kidney disease. Prolonged, regular use of NSAIDs should be discouraged, or if necessary then patient should be monitored regularly.	N/A
Chronic kidney disease and pain	Treatment of pain in patients with renal insufficiency: the World Health Organization three-step ladder adapted(11)	"Because of a significant potential for renal toxicity, use of NSAIDs and COX-2 inhibitors is precarious and relatively contraindicated in patients with renal impairment to any extent."	N/A

Abbreviations: ACCF/ AHA, American College of Cardiology Foundation/ American Heart Association Task Force on Practice Guidelines; AKI, acute kidney injury; CHEP, Canadian Hypertension Education Program; GFR, glomerular filtration rates; KDOQI, Kidney Disease Outcomes Quality Initiative; KDIGO, Kidney Disease Improving Global Outcomes; N/A, not available; NSAIDs, Non-Steroidal Anti-Inflammatory Drugs.

Supplemental Table 2. Previous studies of NSAID use and risk of acute kidney injury and hyperkalemia

Citation	Study design and objective	Study size	Exposure and outcome definitions	Summary of results	Study quality[a]
Studies on NSAID use and risk of AKI					
Bouck 2018(12)	Retrospective cohort study in Ontario, Canada; estimated frequency of NSAID prescriptions among patients at high risk and association between NSAID use and outcomes.	71,124	Exposure: Among high risk patients (code for chronic kidney disease, hypertension or congestive heart failure in past 1 year) with a primary care visit for musculoskeletal issue who have a prescription NSAID within the 7 days following visit compared to matched non-users. Outcomes: Within 37 days of visit, hospitalization with cardiac condition, acute kidney injury, hyperkalemia (based on codes) or death.	NSAIDs were prescribed in approximately 9% of all visits. The prescribing rate decreased by about 2% from 2012 to 2016. Patients with NSAID use had similar event rates to those not on NSAIDs for all outcomes (cardiac 0.8%, acute kidney injury or hyperkalemia 0.1%, and death 0.1%).	Selection **** Comparability ** Outcome **
Zhang 2017(13)	Systematic review and meta-analysis; summarized associations of NSAIDs and AKI risk among the general adult population and patients with CKD.	1.6M general pop from 10 studies; 106,681 CKD patients from 5 studies.	Exposure: All NSAIDs (COX2 and non-selective) were included, but not low-dose aspirin compared to patients with no NSAID use. Outcome/ subgroup: Allowed studies to define AKI and CKD using either lab values or administrative codes.	All included studies summarized in this table. Adjusted pooled OR and 95% CI for general population risk of AKI was 1.73 (1.44-2.07); 8 out of the 10 studies showed a statistically significant association. Unadjusted (adjusted not calculated) pooled OR and 95% CI for CKD population was 1.63 (1.22-2.19); 4 out of 5 found statistically significant associations.	Strong

Citation	Study design and objective	Study size	Exposure and outcome definitions	Summary of results	Study quality[a]
Chou 2016(14)	Nested case-control study in Taiwan; risk of hospitalization with AKI comparing people who used NSAIDs (COX2 and non-selective) to non-users among the general population (CKD patients excluded).	6199 cases; 24,796 controls	Exposure: Current NSAID users (an AKI event during the NSAID prescription period), recent users (AKI 1 to 30 days after the prescription end date), and past users (AKI 31 to 180 days after the prescription end date). Also stratified by COX2 and non-selective NSAIDs. Outcome: Patients hospitalized with a main diagnosis of AKI.	Current users and recent users both had significantly higher OR of hospitalization with AKI, with higher odds among current users. Past users showed a protective effect of AKI. Results were similar when restricted to non-selective NSAIDs; however, there were no significant associations when restricting to COX2 NSAIDs, except for rofecoxib.	Selection ** Comparability ** Exposure ***
Leonard 2012(15)	Case-control study in the UK; association between NSAIDs, PPIs and co-exposure of both drugs with AKI.	27,982 AKI cases, 1,323,850 controls	Exposure: Only PPI, only NSAID, both therapies, or neither; exposure to each drug was calculated based on overlap of day supply with index date. Included both new and prevalent users. Outcome: AKI based on codes and manual review of free-text notes.	NSAIDs alone or in combination with PPI were significant risk factors for AKI in the adjusted analyses (OR 1.31, 95% CI 1.25-1.37 and 1.33, 1.07-1.64 respectively).	Selection **** Comparability ** Exposure ***
Pratt 2010(16)	Retrospective cohort study in Australia; composite risk of hospitalization (with many conditions but including AKI) in the 30 days following an NSAID	16,573 diabetes medications; 17,865 ACEi/ ARB & diuretics; 128,750 general population	Exposure: Among participants prescribed NSAIDs, the 30-day period following the initial prescription was compared to a period prior to receiving the prescription. Outcome: Composite of 30-day hospitalization with AKI, hypertension, coronary heart	Among all three cohorts, NSAID use was associated with greater risk of hospitalization with all conditions. Hospitalization with AKI was significantly greater among the NSAID group for the ACEi/ ARB & diuretic cohort and the	Selection ** Comparability ** Outcome **

Citation	Study design and objective	Study size	Exposure and outcome definitions	Summary of results	Study quality[a]
	prescription, particularly among patients prescribed diabetes medications or those prescribed ACEi/ ARBs and diuretics concurrently.		failure, acute myocardial infarction, or gastrointestinal ulcer based on administrative codes (and then assessed separately for each outcome).	general population cohort.	
Huerta 2005(17)	Nested case-control study in the UK; association between NSAID use and AKI, as well as dose and duration of use. Patients with CKD were excluded.	103 cases; 500 controls	Exposure: Current NSAID use defined as day supply overlapped with index date or if ended in the previous 30 days (also divided into single use vs multiple prescriptions); and categorized into recent user (31-365 days), past user (365+ days previously), and non-user (no recorded use). Outcome: Physician diagnosis of AKI and serum creatinine level (or urea values when creatinine was unavailable) greater than the upper limit of normal.	Current NSAID use had an RR of 3.2 (95% CI 1.8-5.8); risk was slightly higher for high-dose compared to low-dose NSAIDs.	Selection *** Comparability ** Exposure ***

Citation	Study design and objective	Study size	Exposure and outcome definitions	Summary of results	Study quality[a]
Griffin 2000(18)	Nested case-control study in the US; association between NSAID use and AKI among elderly individuals receiving Medicaid.	1791 cases; 9899 controls	Exposure: Current NSAID use; recent use (1-30 days prior to index); past use (31-365 days prior); no use in past 365 days. Also categorized by low, medium and high dose. Outcome: Identification of hospital records with AKI code and review of medical records for serum creatinine values: admission serum creatinine ≥2 mg/dL in combination with either a ≥20% increase in serum creatinine from baseline or ≥20% decline in serum creatinine during hospital.	Current users had an OR of 1.58 for risk of AKI compared to non-users. Recent or past users did not have any increased risk of AKI (based on the first month of use). Among those with underlying CKD, risk of pre-AKI was the same with current NSAID use as those without CKD; however, patients with CKD showed a significant association with AKI. Risk of AKI increased with greater dose of NSAIDs.	Selection **** Comparability ** Exposure ***
Henry 1997(19)	Matched case-control study in Australia; association between NSAIDs and hospitalization with transient renal impairment.	110 cases; 189 controls	Exposure: Structured interviews to ascertain previous exposure to NSAIDs among patients who survived or were well enough to be interviewed. Previous NSAID use was compared to non-use. Outcome: Patients admitted to the hospital with serum creatinine ≥1.7 mg/dL, which improved by ≥20% within the following 14 days or prior to hospital discharge (the first of either two).	Aspirin and NSAID use was higher among cases compared to controls but did not reach statistical significance in the adjusted analyses. There were statistically significant interaction effects for patients with a history of chronic kidney disease.	Selection *** Comparability ** Exposure ***

Citation	Study design and objective	Study size	Exposure and outcome definitions	Summary of results	Study quality[a]
Perez Gutthann 1996(20)	Case-control study in Canada; association between NSAID use and AKI among patients with no pre-existing systemic disease.	28 cases; 1997 controls	Exposure: Current NSAID users (0-30 days), recent users (31-60 days), past users (61-150 days), non-users (no prescription in 150 days prior). Outcome: Combination of diagnostic codes for AKI and chart review for laboratory values.	Current users had an OR (95% CI) of 4.1 (1.5-10.8) compared to non-users. Recent and past users were not significantly associated with AKI; numbers were small. There was a dose response of NSAID use, where risk doubled for high dose versus low dose.	Selection **** Comparability ** Exposure ***
Evans 1995(21)	Case-control study in Scotland; association between NSAID use and hospital admission with AKI (comparisons to community and hospital controls).	207 cases; 411 hospital controls; 1238 community controls	Exposure: Recent exposure to NSAIDS (90 days prior) or previous exposure (NSAID any time after 1989 and before index date, which was between 1990 and 1992). Outcome: Hospitalized with AKI diagnostic code and chart review of laboratory values for renal function at least 20% better than on admission, or if renal function improved by at least 20% with treatment.	Compared to community controls, both recent and any previous exposure to NSAIDs were significantly associated with AKI risk. Compared to hospital controls, only recent exposure was significant.	Selection *** Comparability * Exposure ***
Beard 1992(22)	Matched case-control study in Scotland; risk of AKI associated with NSAIDs.	88 cases; 176 controls	Exposure: Use of NSAIDs in the year prior based on primary care physicians' records compared to non-use in year prior. Outcome: Patients with renal biopsy had medical charts reviewed to identify if they had AKI (*lack of information in abstract on criteria for this*).	31% of cases compared to 22% of controls were on NSAIDs (OR 1.6, 95% CI 0.9-3.0).	Selection ** Comparability * Exposure **

Citation	Study design and objective	Study size	Exposure and outcome definitions	Summary of results	Study quality[a]
Studies on NSAID type and risk of AKI					
Ungprasert 2015(23)	Systematic review and meta-analysis; pooled risks from observational studies of AKI among different types of NSAIDs.	28,992 patients from 5 studies	Exposure: Individual NSAIDs compared to each other. Outcome: Laboratory definition of AKI or administrative codes.	All included studies summarized in this table. Individual NSAIDs significantly associated with risk of AKI included: indomethacin, ibuprofen, naproxen, piroxicam, and sulindac. NSAIDs not significantly associated with AKI included: diclofenac, meloxicam, celecoxib, and rofecoxib.	Moderate
Lafrance 2009(24)	Nested case-control study in the US; risk of hospitalization with AKI comparing selective and non-selective NSAIDs.	22,824 cases; 336,734 controls	Exposure: All patients in cohort received at least one NSAID; exposure status was determined in the period prior to the event (current users had day supply that included the index date; recent users had a prescription in the year prior but not including index date). Outcome: Hospitalization with AKI defined as lab values during hospitalization ≥1.5 times the baseline value in the prior 3 months from hospital admission.	Risk of AKI with NSAID exposure was significant in all exposure categories compared to unexposed patients without recent use, i.e. recent users, current users (single and multiple use). Current users without recent use had an OR of 1.82 (95% CI 1.68-1.98). When looking at each NSAID individually, high dose aspirin had the highest risk of AKI. The following NSAIDs were associated with AKI risk: naproxen, piroxicam, keterolac, etodolac, indomethacin, sulindac, ibuprofen, salsalate; however rofecoxib, celecoxib,	Selection **** Comparability ** Exposure ***

Citation	Study design and objective	Study size	Exposure and outcome definitions	Summary of results	Study quality[a]
				meloxicam, and diclofenac were not. There was a significant interaction between CKD status and NSAID use on AKI.	
Winkelmayer 2008(25)	Retrospective cohort study in the US; short-term use of NSAIDs and the association with AKI, particularly among COX2 inhibitors.	183,446	Exposure: Categorized by type of NSAID used in the 45 days prior to the event (celecoxib was the reference drug); as well as daily dose and number of days supplied. Outcome: Hospitalization with AKI diagnostic code.	After adjusting for multiple comparisons, rofecoxib, ibuprofen, and indomethacin compared to celecoxib were significantly associated with AKI in hospital. Rofecoxib patients with higher doses had a significantly greater risk than lower doses; this dose effect was not observed for ibuprofen or indomethacin users.	Selection **** Comparability ** Outcome **
Zhang 2006(26)	Systematic review and meta-analysis of RCTs; renal effects of COX2 NSAIDs, and separate effects of each drug.	116,094 participants from 114 trials	Exposure: COX2 inhibitors compared to each other: rofecoxib, celecoxib, valdecoxib, parecoxib, etoricoxib, and lumiracoxib. Outcome: A composite of renal events defined as peripheral edema, hypertension or renal	Rofecoxib was the only COX2 that showed significant increased risk of a composite of renal events and renal dysfunction.	Moderate

Citation	Study design and objective	Study size	Exposure and outcome definitions	Summary of results	Study quality[a]
			dysfunction, where the latter was defined as significant changes of serum urea or creatinine level, clinically diagnosed kidney disease, or kidney failure.		
Schneider 2006(27)	Nested case-control study in Canada; association between COX2 and non-selective NSAIDs with AKI.	4228 cases; 84,540 controls	Exposure: Categories included: celecoxib, rofecoxib, meloxicam (COX2), naproxen (non-selective), and conventional NSAIDs (i.e. other non-selective NSAIDs). Each were assessed as low and high dose, and based on time period of exposure (1-30, 31-90 and 91-365 days). Outcome: Hospitalization with diagnosis code for AKI.	Current new users compared to non-users had the greatest risk of AKI: RR 2.05, 95% CI 1.61-2.60. Based on type of NSAID, new users of conventional NSAIDs, rofecoxib, celecoxib and naproxen showed statistically significant risks of AKI. Meloxicam had too few cases to reliably find a difference. Significant dose response was also shown with high versus low dose users.	Selection ** Comparability ** Exposure ***
Guess 1987(28)	Retrospective cohort study in Canada; association between NSAID use and hospitalization with AKI.	29,616 piroxicam; 27,792 ibuprofen; 23,051 naproxen; 22,977 indomethacin; 8333 sulindac; 5615 diclofenac; 833,000 controls	Exposure: NSAID prescriptions from administrative databases compared to patients without NSAID prescriptions. Outcome: Hospitalization with diagnosis code for AKI.	A statistically significant increased risk of AKI was observed for indomethacin and piroxicam but not for ibuprofen, naproxen, sulindac, diclofenac. Results were not adjusted for confounding.	Selection *** Comparability (no stars) Outcome *

Citation	Study design and objective	Study size	Exposure and outcome definitions	Summary of results	Study quality[a]
Studies on NSAID use and risk of hyperkalemia					
Michel 2015(29)	Nested case-control study in the UK; risk factors for hyperkalemia among patients with heart failure.	2176 cases; 4000 controls	Exposure: Current use of NSAIDs (day supply in 30 days prior to and including index date), recent use (day supply ended 31-365 days prior), past use (ended 365+ days prior), and no use. Outcome: 1) serum potassium value ≥10% more than the upper bound of the normal range of the practice's referral laboratory (majority were ≥5.5 mEq/L) or 2) code for 'hyperkalemia' or 'raised serum potassium level' in combination with a referral to a consultant or hospital admission.	Most hyperkalemia cases were managed in primary care. Use of NSAIDs was associated with a significant risk of hyperkalemia, OR 1.41 and 95% CI 1.11-1.79. No significant differences in risk between COX2 and non-selective NSAIDs were found.	Selection **** Comparability ** Exposure ***
LaFrance 2012(30)	Nested case-control study in the US; risk of different NSAIDs on hyperkalemia.	18,326 cases; 355,106 controls	Exposure: Everyone in the study had at least one NSAID prescription at baseline. Exposure was NSAID prescription covering index date: no NSAIDs, 1 NSAID, 2 or more NSAIDs. Separated by specific type of NSAID. Outcome: First serum potassium value ≥6 mEq/L in an outpatient setting or within 48 hours of hospital admission.	NSAID use overall was not associated with hyperkalemia, but specific NSAIDs were: rofecoxib, celecoxib, diclofenac, indomethacin. These associations were not related to COX2 selective agents only.	Selection **** Comparability ** Exposure ***

Citation	Study design and objective	Study size	Exposure and outcome definitions	Summary of results	Study quality[a]
Aljadhey 2012(31)	Retrospective cohort study in Saudi Arabia; association between NSAIDs and increased serum potassium concentrations.	184	Exposure: New use of an NSAID prescription (COX2 and non-selective) compared to paracetamol prescriptions as the control group. Outcome: Serum potassium concentration >5 mEq/L (all patients had to have a baseline serum potassium).	No significant association was found for increased serum potassium risk; although analyses may have been underpowered.	Selection *** Comparability ** Outcome **
Aljadhey 2010(32)	Propensity-score matched retrospective cohort study in the US; COX-2 inhibitors compared to other NSAIDs and the association with increase in serum potassium or abnormal electrocardiogram.	202 COX2; 202 non-COX2 NSAIDs	Exposure: New use of COX2 compared to non-selective NSAIDs (reference group). Outcome: Primary outcome was absolute increase in serum potassium concentration to >5 mEq/L based on the first serum potassium measurement in the 1 year after start of first prescription or 30 days after last dispensed drug (whatever was less); secondary outcome was abnormal electrocardiogram.	OR (95% CI) for a serum potassium increase of >5 mEq/L for COX2 inhibitor compared to non-selective NSAIDs was 2.56 (1.03–6.36). There was no significant difference for having an abnormal electrocardiogram.	Selection *** Comparability ** Outcome **
Nesher 1988(33)	Randomized clinical trial; sulindac compared to indomethacin and risk of hyperkalemia.	74	Exposure: Indomethacin compared to sulindac. Outcome: Mean post-treatment increment in serum potassium	Hyperkalemia developed in three people taking indomethacin and all cases resolved when they were switched to sulindac.	N/A – do not have access to manuscript to assess quality

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; AKI, acute kidney injury; CKD, Chronic Kidney Disease; CI, confidence interval; NSAIDs, Non-Steroidal Anti-Inflammatory Drug; OR, odds ratio; PPI, proton pump inhibitor; RCT, randomized clinical trial.

[a]We assessed study quality using the Newcastle-Ottawa Scale for case-control and cohort studies;(34) maximum quality score is 4 stars for selection, 2 stars for comparability and 3 stars for either exposure (for case-control) or outcome (for cohort). For systematic reviews, we assessed study quality using the Health Evidence™ Quality Assessment Tool – Review Articles;(35) a score of 4 or less is considered weak, 5 to 7 is moderate, and 8 to 10 is strong.

Supplemental Table 3. REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement(36)

	Item No	STROBE items	RECORD items	Reported
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract. (b) Provide in the abstract an informative and balanced summary of what was done and what was found.	(1.1) The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. (1.2) If applicable, the geographic region and time frame within which the study took place should be reported in the title or abstract. (1.3) If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Title and Abstract
Introduction				
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported.		Background
Objectives	3	State specific objectives, including any prespecified hypotheses.		Background
Methods				
Study design	4	Present key elements of study design early in the paper.		Methods • Study Design and Research Setting
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection.		Methods • Study Design and Research Setting • Cohort Assembly and Exposure Categorization • Outcomes
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants.	(6.1) The methods of study population selection (such as codes or algorithms used to	Methods • Study Design and Research Setting

	Item No	STROBE items	RECORD items	Reported
		Describe methods of follow-up. (b) For matched studies, give matching criteria and number of exposed and unexposed.	identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. (6.2) Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. (6.3) If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	• Cohort Assembly and Exposure Categorization
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	(7.1) A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Methods • Cohort Assembly and Exposure Categorization • Outcomes • *Codes for baseline characteristics available upon request*
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group.		Methods • Data Sources
Bias	9	Describe any efforts to address potential sources of bias.		Methods • Statistical Analyses

	Item No	STROBE items	RECORD items	Reported
				Discussion • Study Strengths and Limitations
Study size	10	Explain how the study size was arrived at.		Results • Figure 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why.		Methods • Statistical Analyses
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding. (b) Describe any methods used to examine subgroups and interactions. (c) Explain how missing data were addressed. (d) If applicable, explain how loss to follow-up was addressed. (e) Describe any sensitivity analyses.		Methods • Data Sources • Statistical Analyses
Data access and cleaning methods		N/A	(12.1) Authors should describe the extent to which the investigators had access to the database population used to create the study population. (12.2) Authors should provide information on the data cleaning methods used in the study.	N/A
Linkage		N/A	(12.3) State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	Methods • Study Design and Research Setting • Data sources
Results				

	Item No	STROBE items	RECORD items	Reported
Participants	13	(a) Report numbers of individuals at each stage of study--e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed. (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram.	(13.1) Describe in detail the selection of the persons included in the study (i.e., study population selection), including filtering based on data quality, data availability, and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Results • Figure 1
Descriptive data	14	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders. (b) Indicate number of participants with missing data for each variable of interest. (c) Summarize follow-up time (e.g. average and total amount).		Results • Table 1 • Supplemental Table 7
Outcome data	15	Report numbers of outcome events or summary measures over time.		Results • Table 2
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g. 95% confidence interval). Make clear which confounders were adjusted for and why they were included. (b) Report category boundaries when continuous variables were categorized. (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period.		Results • Table 2

	Item No	STROBE items	RECORD items	Reported
Other analyses	17	Report other analyses done (e.g. analyses of subgroups and interactions, and sensitivity analyses).		Results • Figure 2 • Supplemental Figure 1
Key results	18	Summarize key results with reference to study objectives.		Discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	(19.1) Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Discussion • Study Strengths and Limitations
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.		Discussion
Generalizability	21	Discuss the generalizability (external validity) of the study results.		Discussion • Study Strengths and Limitations
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based.		Funding Declaration
Accessibility of protocol, raw data, and programming code		N/A	(22.1) Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Availability of Data and Materials

Supplemental Table 4. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) statement(37)

Section/Topic	Item	Checklist Item	Reported
Title and abstract			
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	N/A (title focuses on first part of study)
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	Abstract
Introduction			
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	Background
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	Background
Methods			
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	Methods • Study Design and Research Setting • Data Sources
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	Methods • Cohort Assembly and Exposure Categorization
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	Methods • Study Design and Research Setting
	5b	Describe eligibility criteria for participants.	Methods • Cohort Assembly and Exposure Categorization
	5c	Give details of treatments received, if relevant.	Methods • Cohort Assembly and Exposure Categorization
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	Methods • Outcomes
	6b	Report any actions to blind assessment of the	N/A

		outcome to be predicted.	(administrative data)
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	Methods • Statistical Analyses
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	N/A (administrative data)
Sample size	8	Explain how the study size was arrived at.	N/A (population-based study)
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	N/A (no missing data for predictors)
Statistical analysis methods	10a	Describe how predictors were handled in the analyses.	Methods • Statistical Analyses
	10b	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	Methods • Statistical Analyses
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	Methods • Statistical Analyses
Risk groups	11	Provide details on how risk groups were created, if done.	N/A
Results			
Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	Results • Figure 1
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	Results • Table 1
Model development	14a	Specify the number of participants and outcome events in each analysis.	Results
	14b	If done, report the unadjusted association between each candidate predictor and outcome.	N/A
Model specification	15a	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	Results • Supplemental Table 8
	15b	Explain how to the use the prediction model.	Results • Supplemental Table 9 Discussion
Model performance	16	Report performance measures (with CIs) for the prediction model.	Results • Figure 3 • Supplemental Figure 2

			• Supplemental Table 9
Discussion			
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	Discussion • Study Strengths and Limitations
Interpretation	19b	Give an overall interpretation of the results, considering objectives, limitations, and results from similar studies, and other relevant evidence.	Discussion
Implications	20	Discuss the potential clinical use of the model and implications for future research.	Discussion
Other information			
Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	Results
Funding	22	Give the source of funding and the role of the funders for the present study.	Funding Declaration

Supplemental Table 5. Prescription NSAIDs included in the study

Drug name	% of NSAID users in cohort
Non-Selective NSAIDs	
Diclofenac	0.2%
Diclofenac Sodium	5%
Diclofenac Sodium & Misoprostol	11%
Diflunisal	0.04%
Floctafenine	0.02%
Flurbiprofen	0.1%
Ibuprofen	6%
Indomethacin	3%
Ketoprofen	0.1%
Mefenamic Acid	0.08%
Naproxen	24%
Piroxicam	0.09%
Sulindac	0.2%
Tiaprofenic Acid	0.1%
COX-2 Inhibitors	
Celecoxib	22%
Meloxicam	28%

Supplemental Table 6. 2012 KDIGO thresholds for acute kidney injury stages(38)

Stage	Definition
1	50 to <100% increase in serum creatinine from baseline or an absolute increase ≥0.3 mg/dL, but does not meet stage two or three criteria
2	100 to <200% increase from baseline
3	≥200% increase from baseline, absolute serum creatinine value of 4.0 mg/dL, or receipt of acute dialysis

Supplemental Table 7. All baseline characteristics for the NSAID user and non-user groups before and after matching

Variable	Value	Baselines Pre-Match			Baselines Post-Match		
		NSAID users n=61,219	Non-users n=156,589	Stan. Diff.	NSAID users n=46,107	Non-users n=46,107	Stan. Diff.
Demographics							
Year of index date, No. (%)	2008 & 2009	860 (1.4)	38 (0.0)	0.1	11 (0.0)	19 (0.0)	0.00
	2010	755 (1.2)	71 (0.0)	0.16	43 (0.1)	37 (0.1)	0.00
	2011	855 (1.4)	104 (0.1)	0.15	55 (0.1)	50 (0.1)	0.00
	2012	1,321 (2.2)	240 (0.2)	0.18	129 (0.3)	156 (0.3)	0.00
	2013	5,453 (8.9)	3,622 (2.3)	0.29	2,148 (4.7)	2,327 (5.0)	0.01
	2014	28,852 (47.1)	75,953 (48.5)	0.03	23,592 (51.2)	23,404 (50.8)	0.01
	2015	23,123 (37.8)	76,561 (48.9)	0.23	20,129 (43.7)	20,114 (43.6)	0.00
Age, year	Mean ± SD	74.1 (6.4)	76.0 (8.1)	0.27	74.2 (6.5)	74.2 (7.1)	0.01
	Median (IQR)	73 (69-78)	75 (69-82)		73 (69-78)	72 (68-79)	
	66-74	35,651 (58.2)	78,030 (49.8)	0.17	26,745 (58.0)	26,859 (58.3)	0.01
	75-84	20,860 (34.1)	50,562 (32.3)	0.04	15,502 (33.6)	14,590 (31.6)	0.04
	85+	4,708 (7.7)	27,997 (17.9)	0.31	3,860 (8.4)	4,658 (10.1)	0.06
Sex, No. (%)	Female	36,016 (58.8)	84,355 (53.9)	0.10	26,654 (57.8)	26,552 (57.6)	0.00
Rural status, No. (%)[a]	Y	3,489 (5.7)	8,431 (5.4)	0.01	2,298 (5.0)	2,334 (5.1)	0.00
LHIN, No. (%)	1	95 (0.2)	323 (0.2)	0.00	87 (0.2)	96 (0.2)	0.00
	2	8,684 (14.2)	24,222 (15.5)	0.04	6,006 (13.0)	6,346 (13.8)	0.02
	3	32 (0.1)	168 (0.1)	0.00	23 (0.0)	22 (0.0)	0.02
	4	85 (0.1)	220 (0.1)	0.00	62 (0.1)	66 (0.1)	0.00
	5	4,472 (7.3)	6,863 (4.4)	0.12	3,164 (6.9)	3,021 (6.6)	0.01
	6	8,614 (14.1)	20,482 (13.1)	0.03	6,482 (14.1)	6,494 (14.1)	0.00
	7	7,387 (12.1)	23,733 (15.2)	0.09	6,279 (13.6)	6,218 (13.5)	0.00
	8	12,405 (20.3)	30,522 (19.5)	0.02	9,467 (20.5)	9,392 (20.4)	0.00

Variable	Value	Baselines Pre-Match			Baselines Post-Match		
		NSAID users n=61,219	Non-users n=156,589	Stan. Diff.	NSAID users n=46,107	Non-users n=46,107	Stan. Diff.
	9	15,196 (24.8)	39,421 (25.2)	0.01	11,052 (24.0)	10,958 (23.8)	0.00
	10	32 (0.1)	116 (0.1)	0.00	24 (0.1)	24 (0.1)	0.00
	11	115 (0.2)	270 (0.2)	0.00	91 (0.2)	88 (0.2)	0.00
	12	310 (0.5)	1,027 (0.7)	0.03	268 (0.6)	293 (0.6)	0.00
	13 & 14	3,792 (6.2)	9,222 (5.9)	0.01	3,102 (6.7)	3,089 (6.7)	0.00
Income quintile, No. (%)[b]	1	11,523 (18.8)	26,116 (16.7)	0.05	8,337 (18.1)	8,234 (17.9)	0.01
	2	12,365 (20.2)	29,469 (18.8)	0.04	9,215 (20.0)	9,055 (19.6)	0.01
	3	12,823 (20.9)	31,049 (19.8)	0.03	9,510 (20.6)	9,457 (20.5)	0.00
	4	12,653 (20.7)	33,721 (21.5)	0.02	9,622 (20.9)	9,680 (21.0)	0.00
	5	11,855 (19.4)	36,234 (23.1)	0.09	9,423 (20.4)	9,681 (21.0)	0.01
Long term care home, No. (%)		128 (0.2)			103 (0.2)		
Index prescription information							
Index NSAID is a COX2 inhibitor, No. (%)		30,741 (50.2)			23,208 (50.3)		
Percentage of maximum daily dose	Mean ± SD	61.9 (28.3)			61.5 (28.2)		
	Median (IQR)	60 (37.5-90.0)			60 (37,5-83.3)		
Prescribing physician characteristics							
Age, year	Missing, No. (%)	3,256 (5.3)			2,395 (5.2)		
	Mean ± SD	55.6 (11.3)			55.8 (11.3)		
	Median (IQR)	56 (47-64)			57 (48-64)		
Sex, No. (%)	Missing	2,620 (4.3)			1,862 (4.0)		
	F	15,972 (26.1)			12,019 (26.1)		
	M	42,627 (69.6)			32,226 (69.9)		
Rural status, No. (%)	Missing	2,574 (4.2)			1,827 (4.0)		

Variable	Value	Baselines Pre-Match			Baselines Post-Match		
		NSAID users n=61,219	Non-users n=156,589	Stan. Diff.	NSAID users n=46,107	Non-users n=46,107	Stan. Diff.
	N	55,926 (91.4)			42,502 (92.2)		
	Y	2,719 (4.4)			1,778 (3.9)		
Time since graduation, year	Missing, No. (%)	2,624 (4.3)			2,624 (5.7)		
	Mean ± SD	29.0 (11.8)			29.2 (11.9)		
	Median (IQR)	30 (21-37)			30 (21-38)		
Canadian medical graduate, No. (%)	Missing	3,256 (5.3)			2,395 (5.2)		
	0	21,010 (34.3)			15,709 (34.1)		
	1	36,953 (60.4)			28,003 (60.7)		
Medical specialty, No. (%)	Missing	2,572 (4.2)			1,825 (4.0)		
	Nephrologist	54 (0.1)			38 (0.1)		
	Primary care	52,772 (86.2)			40,040 (86.8)		
	Cardiologist	127 (0.2)			107 (0.2)		
	Other	5,694 (9.3)			4,097 (8.9)		
Reimbursement type, No. (%)	Not primary care physician or missing	11,645 (19.0)			8,670 (18.8)		
	Comprehensive Care Model	2,700 (4.4)			2,156 (4.7)		
	Family Health Group	26,804 (43.8)			20,080 (43.6)		
	Family Health Network	1,061 (1.7)			750 (1.6)		
	Family Health Organization	18,409 (30.1)			13,960 (30.3)		
	Other	600 (1.0)			491 (1.1)		

Variable	Value	Baselines Pre-Match			Baselines Post-Match		
		NSAID users n=61,219	Non-users n=156,589	Stan. Diff.	NSAID users n=46,107	Non-users n=46,107	Stan. Diff.
Healthcare use in previous year							
Number of hospitalizations	Mean ± SD	0.2 (0.5)	0.2 (0.6)	0.11	0.1 (0.5)	0.1 (0.5)	0.00
	Median (IQR)	0 (0-0)	0 (0-0)		0 (0-0)	0 (0-0)	
Number of hospitalizations, No. (%)	0	54,224 (88.6)	133,250 (85.1)	0.10	41,021 (89.0)	41,042 (89.0)	0.00
	1	5,534 (9.0)	16,960 (10.8)	0.06	3,988 (8.6)	3,988 (8.6)	0.00
	2+	1,461 (2.4)	6,379 (4.1)	0.10	1,098 (2.4)	1,077 (2.3)	0.01
Number of emergency department visits	Mean ± SD	0.5 (1.2)	0.5 (1.1)	0.03	0.5 (1.2)	0.5 (1.1)	0.01
	Median (IQR)	0 (0-1)	0 (0-1)		0 (0-1)	0 (0-1)	
Number of emergency department visits, No. (%)	0	44,193 (72.2)	115,164 (73.5)	0.03	33,954 (73.6)	33,862 (73.4)	0.00
	1-2	14,094 (23.0)	34,933 (22.3)	0.02	10,183 (22.1)	10,357 (22.5)	0.01
	3-4	2,092 (3.4)	4,848 (3.1)	0.02	1,417 (3.1)	1,440 (3.1)	0.00
	5+	840 (1.4)	1,644 (1.0)	0.04	553 (1.2)	448 (1.0)	0.02
Number of family physician visits	Mean ± SD	9.2 (7.4)	8.9 (9.4)	0.04	8.8 (7.2)	8.7 (8.0)	0.02
	Median (IQR)	8 (5-11)	6 (4-11)		7 (5-11)	7 (4-11)	
Number of family physician visits, No. (%)	0	857 (1.4)	3,967 (2.5)	0.08	734 (1.6)	779 (1.7)	0.01
	1-3	7,543 (12.3)	31,252 (20.0)	0.21	6,334 (13.7)	7,739 (16.8)	0.09
	4-6	16,685 (27.3)	44,673 (28.5)	0.03	13,291 (28.8)	13,636 (29.6)	0.02
	7+	36,134 (59.0)	76,697 (49.0)	0.20	25,748 (55.8)	23,953 (52.0)	0.08
Number of nephrologist visits	Mean ± SD	0.1 (0.6)	0.2 (1.0)	0.15	0.1 (0.6)	0.1 (0.5)	0.00
	Median (IQR)	0 (0-0)	0 (0-0)		0 (0-0)	0 (0-0)	
Number of nephrologist visits, No. (%)	0	57,971 (94.7)	141,619 (90.4)	0.16	43,530 (94.4)	43,349 (94.0)	0.02

Variable	Value	Baselines Pre-Match			Baselines Post-Match		
		NSAID users n=61,219	Non-users n=156,589	Stan. Diff.	NSAID users n=46,107	Non-users n=46,107	Stan. Diff.
	1	1,919 (3.1)	6,662 (4.3)	0.06	1,496 (3.2)	1,655 (3.6)	0.02
	2+	1,329 (2.2)	8,308 (5.3)	0.16	1,081 (2.3)	1,103 (2.4)	0.01
Number of internist visits	Mean ± SD	0.7 (2.3)	0.9 (3.5)	0.09	0.7 (2.4)	0.6 (2.4)	0.00
	Median (IQR)	0 (0-0)	0 (0-0)		0 (0-0)	0 (0-0)	
Number of internist visits, No. (%)	0	46,873 (76.6)	118,037 (75.4)	0.03	35,797 (77.6)	35,780 (77.6)	0.00
	1-2	9,955 (16.3)	23,901 (15.3)	0.03	7,050 (15.3)	7,124 (15.5)	0.01
	3+	4,391 (7.2)	14,651 (9.4)	0.08	3,260 (7.1)	3,203 (6.9)	0.01
Number of oncologist visits	Mean ± SD	0.3 (2.4)	0.4 (3.1)	0.04	0.3 (2.4)	0.3 (2.6)	0.00
	Median (IQR)	0 (0-0)	0 (0-0)		0 (0-0)	0 (0-0)	
Number of oncologist visits, No. (%)	0	57,600 (94.1)	145,899 (93.2)	0.04	43,314 (93.9)	43,395 (94.1)	0.01
	1	1,267 (2.1)	3,634 (2.3)	0.01	968 (2.1)	999 (2.2)	0.01
	2+	2,352 (3.8)	7,056 (4.5)	0.04	1,825 (4.0)	1,713 (3.7)	0.02
Number of cardiologist visits	Mean ± SD	1.0 (2.0)	1.4 (2.9)	0.16	1.0 (2.0)	1.0 (2.0)	0.01
	Median (IQR)	0 (0-1)	0 (0-2)		0 (0-1)	0 (0-1)	
Number of cardiologist visits, No. (%)	0	35,055 (57.3)	82,507 (52.7)	0.09	26,268 (57.0)	25,830 (56.0)	0.02
	1	13,569 (22.2)	32,655 (20.9)	0.03	10,194 (22.1)	10,065 (21.8)	0.01
	2+	12,595 (20.6)	41,427 (26.5)	0.14	9,645 (20.9)	10,212 (22.1)	0.03
Preventative healthcare when indicated							
Flu shot in past 2 years, No. (%)		38,463 (62.8)	87,973 (56.2)	0.13	28,037 (60.8)	27,970 (60.7)	0.00
Fecal occult blood test in past 2 years, No. (%)	N/A	25,568 (41.8)	78,559 (50.2)	0.17	19,362 (42.0)	19,248 (41.7)	0.01
	Yes	14,553 (23.8)	29,914 (19.1)	0.11	10,581 (22.9)	10,648 (23.1)	0.00

Variable	Value	Baselines Pre-Match			Baselines Post-Match		
		NSAID users n=61,219	Non-users n=156,589	Stan. Diff.	NSAID users n=46,107	Non-users n=46,107	Stan. Diff.
	No	21,098 (34.5)	48,116 (30.7)	0.08	16,164 (35.1)	16,211 (35.2)	0.00
Papanicolaou test in past 3 years, No. (%)	N/A	50,858 (83.1)	133,603 (85.3)	0.06	38,096 (82.6)	37,908 (82.2)	0.01
	Yes	5,324 (8.7)	11,937 (7.6)	0.04	4,160 (9.0)	4,277 (9.3)	0.01
	No	5,037 (8.2)	11,049 (7.1)	0.04	3,851 (8.4)	3,922 (8.5)	0.00
Mammogram in past 3 years, No. (%)	N/A	40,812 (66.7)	116,903 (74.7)	0.18	31,087 (67.4)	31,063 (67.4)	0.00
	Yes	14,690 (24.0)	29,735 (19.0)	0.11	11,401 (24.7)	11,407 (24.7)	0.00
	No	5,717 (9.3)	9,951 (6.4)	0.12	3,619 (7.8)	3,637 (7.9)	0.00
Tdap vaccine in past 5 years, No. (%)		4,755 (7.8)	13,789 (8.8)	0.04	3,936 (8.5)	3,964 (8.6)	0.00
Comorbidity in past 5 years, No. (%) (unless otherwise specified)							
Charlson comorbidity score, No. (%)	0	46,909 (76.6)	104,469 (66.7)	0.22	35,055 (76.0)	34,918 (75.7)	0.01
	1	6,668 (10.9)	19,989 (12.8)	0.06	5,017 (10.9)	5,089 (11.0)	0.00
	2	4,426 (7.2)	15,417 (9.8)	0.09	3,442 (7.5)	3,493 (7.6)	0.00
	3	3,216 (5.3)	16,714 (10.7)	0.20	2,593 (5.6)	2,607 (5.7)	0.00
John Hopkins ADG Score	Mean ± SD	12.4 (4.0)	11.6 (4.2)	0.18	12.1 (4.0)	12.1 (4.0)	0.01
	Median (IQR)	12 (10-15)	12 (9-15)		12 (9-15)	12 (9-15)	
	0-4	1,524 (2.5)	7,421 (4.7)	0.12	1,377 (3.0)	1,396 (3.0)	0.00
	5-9	13,081 (21.4)	41,717 (26.6)	0.12	10,850 (23.5)	10,840 (23.5)	0.00
	10-14	27,900 (45.6)	67,193 (42.9)	0.05	20,931 (45.4)	21,065 (45.7)	0.01
	15-19	16,500 (27.0)	35,671 (22.8)	0.10	11,494 (24.9)	11,406 (24.7)	0.00
	20+	2,214 (3.6)	4,587 (2.9)	0.04	1,455 (3.2)	1,400 (3.0)	0.01
Hyponatremia		651 (1.1)	3,013 (1.9)	0.07	535 (1.2)	528 (1.1)	0.01
Ischemic heart disease		15,950 (26.1)	49,501 (31.6)	0.12	12,150 (26.4)	12,265 (26.6)	0.00

Variable	Value	Baselines Pre-Match			Baselines Post-Match		
		NSAID users n=61,219	Non-users n=156,589	Stan. Diff.	NSAID users n=46,107	Non-users n=46,107	Stan. Diff.
Congestive heart failure		4,105 (6.7)	21,268 (13.6)	0.23	3,178 (6.9)	3,269 (7.1)	0.01
Cardiac arrhythmia		9,867 (16.1)	40,410 (25.8)	0.24	7,805 (16.9)	8,021 (17.4)	0.01
Ventricular arrhythmia		91 (0.1)	791 (0.5)	0.07	71 (0.2)	76 (0.2)	0.00
Myocardial infarction		2,119 (3.5)	8,828 (5.6)	0.10	1,634 (3.5)	1,686 (3.7)	0.01
Cardiac arrest		184 (0.3)	1,058 (0.7)	0.06	139 (0.3)	143 (0.3)	0.00
Peripheral vascular disease		2,320 (3.8)	7,572 (4.8)	0.05	1,752 (3.8)	1,736 (3.8)	0.00
Atrial fibrillation		1,548 (2.5)	12,489 (8.0)	0.25	1,277 (2.8)	1,407 (3.1)	0.02
Coronary artery bypass graft		570 (0.9)	2,301 (1.5)	0.06	450 (1.0)	479 (1.0)	0.00
Percutaneous coronary intervention		1,360 (2.2)	4,957 (3.2)	0.06	1,091 (2.4)	1,093 (2.4)	0.00
Pacemaker		5,689 (9.3)	21,443 (13.7)	0.14	4,596 (10.0)	4,601 (10.0)	0.00
Diabetes		22,177 (36.2)	57,397 (36.7)	0.01	16,653 (36.1)	16,610 (36.0)	0.00
Hypertension		46,410 (75.8)	116,542 (74.4)	0.03	34,526 (74.9)	34,391 (74.6)	0.01
Hypotension		559 (0.9)	2,718 (1.7)	0.07	430 (0.9)	414 (0.9)	0.00
Chronic liver disease		642 (1.0)	2,455 (1.6)	0.05	509 (1.1)	519 (1.1)	0.00
Liver transplant		9 (0.0)	99 (0.1)	0.04	7 (0.0)	7 (0.0)	0.00
Inflammatory bowel disease		912 (1.5)	2,795 (1.8)	0.02	712 (1.5)	749 (1.6)	0.01
Peptic ulcer		14,206 (23.2)	27,461 (17.5)	0.14	9,983 (21.7)	9,921 (21.5)	0.00
Acute pancreatitis		669 (1.1)	2,077 (1.3)	0.02	500 (1.1)	514 (1.1)	0.00
Chronic pancreatitis		100 (0.2)	378 (0.2)	0.00	78 (0.2)	65 (0.1)	0.03
Appendicitis		352 (0.6)	730 (0.5)	0.01	251 (0.5)	245 (0.5)	0.00
Hernia		1,429 (2.3)	3,680 (2.4)	0.01	1,068 (2.3)	1,067 (2.3)	0.00
Gallstones		2,628 (4.3)	6,122 (3.9)	0.02	1,956 (4.2)	1,926 (4.2)	0.00
Kidney stones		2,418 (3.9)	5,925 (3.8)	0.01	1,748 (3.8)	1,760 (3.8)	0.00
Acute urinary retention		919 (1.5)	3,547 (2.3)	0.06	718 (1.6)	707 (1.5)	0.01

Variable	Value	Baselines Pre-Match			Baselines Post-Match		
		NSAID users n=61,219	Non-users n=156,589	Stan. Diff.	NSAID users n=46,107	Non-users n=46,107	Stan. Diff.
Respiratory infection		31,353 (51.2)	60,406 (38.6)	0.26	22,548 (48.9)	22,335 (48.4)	0.01
Chronic obstructive pulmonary disease, emphysema or chronic bronchitis		7,001 (11.4)	19,576 (12.5)	0.03	5,097 (11.1)	5,091 (11.0)	0.00
Chronic lung disease		14,709 (24.0)	34,723 (22.2)	0.04	10,473 (22.7)	10,403 (22.6)	0.00
Malignancy		7,407 (12.1)	21,501 (13.7)	0.05	5,669 (12.3)	5,657 (12.3)	0.00
Human immunodeficiency virus		62 (0.1)	243 (0.2)	0.03	49 (0.1)	42 (0.1)	0.00
Sexually transmitted diseases		1,378 (2.3)	2,503 (1.6)	0.05	956 (2.1)	960 (2.1)	0.00
Osteoporosis		10,193 (16.7)	23,428 (15.0)	0.05	7,570 (16.4)	7,519 (16.3)	0.00
Joint disease		34,669 (56.6)	44,363 (28.3)	0.60	23,064 (50.0)	22,681 (49.2)	0.02
Joint disorder		7,378 (12.1)	9,779 (6.2)	0.21	4,706 (10.2)	4,572 (9.9)	0.01
Bursitis		18,345 (30.0)	23,268 (14.9)	0.37	11,902 (25.8)	11,626 (25.2)	0.01
Muscular dystrophy		132 (0.2)	330 (0.2)	0.00	81 (0.2)	88 (0.2)	0.00
Fibromyalgia		4,417 (7.2)	5,305 (3.4)	0.17	2,686 (5.8)	2,514 (5.5)	0.01
Muscoskeletal disorder		20,930 (34.2)	39,486 (25.2)	0.20	14,452 (31.3)	14,165 (30.7)	0.01
Muscoskeletal symptoms		6,792 (11.1)	9,563 (6.1)	0.18	4,192 (9.1)	4,012 (8.7)	0.01
Torticollis		133 (0.2)	143 (0.1)	0.03	66 (0.1)	62 (0.1)	0.00
Acute sprain		27,976 (45.7)	45,482 (29.0)	0.35	19,151 (41.5)	18,898 (41.0)	0.01
Fracture		7,630 (12.5)	20,413 (13.0)	0.01	5,634 (12.2)	5,558 (12.1)	0.00
Digit fracture		1,212 (2.0)	2,686 (1.7)	0.02	885 (1.9)	890 (1.9)	0.00
Hip fracture		531 (0.9)	3,297 (2.1)	0.10	436 (0.9)	454 (1.0)	0.01
Congenital limb disorder		48 (0.1)	93 (0.1)	0.00	33 (0.1)	36 (0.1)	0.00
Foot deformity		2,138 (3.5)	3,253 (2.1)	0.08	1,430 (3.1)	1,413 (3.1)	0.00

Variable	Value	Baselines Pre-Match			Baselines Post-Match		
		NSAID users n=61,219	Non-users n=156,589	Stan. Diff.	NSAID users n=46,107	Non-users n=46,107	Stan. Diff.
Back pain		30,486 (49.8)	41,164 (26.3)	0.50	20,383 (44.2)	20,051 (43.5)	0.01
Kyphoscoliosis		351 (0.6)	485 (0.3)	0.04	221 (0.5)	210 (0.5)	0.00
Capsulitis		28 (0.0)	29 (0.0)	0.04	17 (0.0)	15 (0.0)	0.00
Surgical care		6,919 (11.3)	19,027 (12.2)	0.03	5,120 (11.1)	5,151 (11.2)	0.00
Back surgery		790 (1.3)	836 (0.5)	0.08	454 (1.0)	428 (0.9)	0.01
Knee surgery		3,829 (6.3)	3,755 (2.4)	0.19	2,221 (4.8)	2,130 (4.6)	0.01
Hip surgery		1,612 (2.6)	2,604 (1.7)	0.06	1,091 (2.4)	1,091 (2.4)	0.00
Amputation		73 (0.1)	233 (0.1)	0.00	59 (0.1)	46 (0.1)	0.00
Cerebrovascular disease		4,783 (7.8)	20,211 (12.9)	0.17	3,765 (8.2)	3,778 (8.2)	0.00
Parkinsons		845 (1.4)	3,570 (2.3)	0.07	680 (1.5)	650 (1.4)	0.01
Seizure		869 (1.4)	3,633 (2.3)	0.07	671 (1.5)	651 (1.4)	0.01
Multiple sclerosis		163 (0.3)	633 (0.4)	0.02	129 (0.3)	124 (0.3)	0.00
Dementia		3,729 (6.1)	24,123 (15.4)	0.30	3,142 (6.8)	3,106 (6.7)	0.00
Headache		1,729 (2.8)	3,337 (2.1)	0.05	1,189 (2.6)	1,173 (2.5)	0.01
Migraine		2,649 (4.3)	4,491 (2.9)	0.08	1,801 (3.9)	1,804 (3.9)	0.00
Concussion		518 (0.8)	1,248 (0.8)	0.00	366 (0.8)	354 (0.8)	0.00
Gout		4,985 (8.1)	4,581 (2.9)	0.23	2,804 (6.1)	2,426 (5.3)	0.03
Rheumatoid arthritis		3,994 (6.5)	4,517 (2.9)	0.17	2,436 (5.3)	2,320 (5.0)	0.01
Osteoarthritis		7,031 (11.5)	7,861 (5.0)	0.24	4,245 (9.2)	4,163 (9.0)	0.01
Laceration		6,582 (10.8)	19,076 (12.2)	0.04	4,873 (10.6)	4,823 (10.5)	0.00
Skin ulcer		521 (0.9)	2,766 (1.8)	0.08	413 (0.9)	421 (0.9)	0.00
Burns		1,341 (2.2)	2,638 (1.7)	0.04	955 (2.1)	916 (2.0)	0.01
Endometriosis	N/A	25,203 (41.2)	72,234 (46.1)	0.10	26,562 (57.6)	26,458 (57.4)	0.00
	Yes	35,879 (58.6)	84,150 (53.7)	0.10	92 (0.2)	94 (0.2)	0.00
	No	137 (0.2)	205 (0.1)	0.03	19,453 (42.2)	19,555 (42.4)	0.00

Variable	Value	Baselines Pre-Match			Baselines Post-Match		
		NSAID users n=61,219	Non-users n=156,589	Stan. Diff.	NSAID users n=46,107	Non-users n=46,107	Stan. Diff.
Cervical pain	N/A	25,203 (41.2)	72,234 (46.1)	0.10	26,196 (56.8)	26,130 (56.7)	0.00
	Yes	35,266 (57.6)	83,531 (53.3)	0.09	458 (1.0)	422 (0.9)	0.01
	No	750 (1.2)	824 (0.5)	0.08	19,453 (42.2)	19,555 (42.4)	0.00
Sciatica		21,449 (35.0)	26,131 (16.7)	0.43	13,872 (30.1)	13,479 (29.2)	0.02
Shingles		3,514 (5.7)	7,641 (4.9)	0.04	2,587 (5.6)	2,563 (5.6)	0.00
Neuralgia		830 (1.4)	1,569 (1.0)	0.04	562 (1.2)	534 (1.2)	0.00
Pain		32,285 (52.7)	54,717 (34.9)	0.36	22,548 (48.9)	22,434 (48.7)	0.00
Schizophrenia		704 (1.1)	3,766 (2.4)	0.10	576 (1.2)	580 (1.3)	0.01
Personality disorder		403 (0.7)	1,051 (0.7)	0.00	286 (0.6)	288 (0.6)	0.00
Depression		5,161 (8.4)	13,267 (8.5)	0.00	3,729 (8.1)	3,766 (8.2)	0.00
Bipolar disorder		103 (0.2)	485 (0.3)	0.02	79 (0.2)	75 (0.2)	0.00
Psychologic signs and symptoms		587 (1.0)	3,500 (2.2)	0.10	477 (1.0)	478 (1.0)	0.00
Other psychosocial disorders		150 (0.2)	293 (0.2)	0.00	110 (0.2)	110 (0.2)	0.00
Healthcare procedures in past 1 year (unless otherwise indicated), No. (%)							
Carotid ultrasound		2,812 (4.6)	8,492 (5.4)	0.04	2,179 (4.7)	2,230 (4.8)	0.00
Coronary angiogram		1,005 (1.6)	3,557 (2.3)	0.05	785 (1.7)	797 (1.7)	0.00
Coronary revascularization		415 (0.7)	1,731 (1.1)	0.04	344 (0.7)	359 (0.8)	0.01
Echocardiogram		12,466 (20.4)	37,234 (23.8)	0.08	9,526 (20.7)	9,649 (20.9)	0.00
Holter test		4,684 (7.7)	14,820 (9.5)	0.06	3,616 (7.8)	3,675 (8.0)	0.01
Stress test		8,472 (13.8)	19,822 (12.7)	0.03	6,223 (13.5)	6,213 (13.5)	0.00
Aneurysm repair		17 (0.0)	73 (0.0)	0.03	10 (0.0)	13 (0.0)	0.00
Cardiac catheterization		1,032 (1.7)	3,699 (2.4)	0.05	807 (1.8)	819 (1.8)	0.00
Electroencephalogram		257 (0.4)	1,015 (0.6)	0.03	212 (0.5)	189 (0.4)	0.01
Deep vein thrombosis / pulmonary embolism		103 (0.2)	512 (0.3)	0.02	81 (0.2)	84 (0.2)	0.00

Variable	Value	Baselines Pre-Match			Baselines Post-Match		
		NSAID users n=61,219	Non-users n=156,589	Stan. Diff.	NSAID users n=46,107	Non-users n=46,107	Stan. Diff.
Electrocardiography		32,951 (53.8)	85,660 (54.7)	0.02	24,611 (53.4)	24,589 (53.3)	0.00
Bone mineral density test		23,637 (38.6)	50,132 (32.0)	0.14	17,401 (37.7)	17,301 (37.5)	0.00
Hearing test		10,787 (17.6)	24,557 (15.7)	0.05	7,894 (17.1)	8,034 (17.4)	0.01
Cystoscopy		7,602 (12.4)	19,071 (12.2)	0.01	5,642 (12.2)	5,676 (12.3)	0.00
Computed tomography scan - head		14,304 (23.4)	44,891 (28.7)	0.12	10,764 (23.3)	10,610 (23.0)	0.01
Computed tomography scan - other		21,596 (35.3)	56,290 (35.9)	0.01	15,901 (34.5)	15,918 (34.5)	0.00
Xray - back		29,048 (47.4)	44,677 (28.5)	0.40	19,685 (42.7)	19,347 (42.0)	0.01
Xray - neck		574 (0.9)	1,115 (0.7)	0.02	411 (0.9)	410 (0.9)	0.00
Xray - chest		42,911 (70.1)	108,674 (69.4)	0.02	31,597 (68.5)	31,600 (68.5)	0.00
Lung function		13,810 (22.6)	34,269 (21.9)	0.02	10,184 (22.1)	10,304 (22.3)	0.00
Sputum		779 (1.3)	1,876 (1.2)	0.01	584 (1.3)	577 (1.3)	0.00
At least one albumin-to-creatinine test in past 1 year		35,803 (58.5)	79,468 (50.7)	0.16	26,481 (57.4)	26,330 (57.1)	0.01
At least one albumin-to-creatinine test in past 2 years		42,172 (68.9)	97,394 (62.2)	0.14	31,300 (67.9)	31,187 (67.6)	0.01
Laboratory test values in the past 1 year							
Time from baseline serum creatinine to index date	Mean ± SD	120.5 (101.2)	115.8 (97.2)	0.05	120.6 (101.7)	121.0 (98.5)	0.00
	Median (IQR)	94 (33-192)	88 (34-179)		94 (32-193)	95 (37-187)	
Baseline serum creatinine value, mg/dL	Mean ± SD	0.9 (0.3)	1.0 (0.4)	0.27	0.9 (0.3)	0.9 (0.3)	0.00
	Median (IQR)	76 (65-91)	80 (67-97)		76 (65-91)	77 (65-91)	

Variable	Value	Baselines Pre-Match			Baselines Post-Match		
		NSAID users n=61,219	Non-users n=156,589	Stan. Diff.	NSAID users n=46,107	Non-users n=46,107	Stan. Diff.
Baseline eGFR value, mL/min/1.73 m^2	Mean ± SD	73.0 (16.0)	69.1 (18.6)	0.23	73.0 (16.0)	73.0 (16.0)	0.00
	Median (IQR)	75 (62-86)	72 (57-84)		75 (62-86)	75 (62-86)	
Baseline eGFR value, mL/min/1.73 m^2, No. (%)	60+	48,159 (78.7)	110,350 (70.5)	0.19	36,208 (78.5)	36,208 (78.5)	0.00
	45-<60	9,448 (15.4)	27,333 (17.5)	0.06	7,096 (15.4)	7,096 (15.4)	0.00
	<45	3,612 (5.9)	18,906 (12.1)	0.22	2,803 (6.1)	2,803 (6.1)	0.00
Baseline potassium value, mEq/L	Mean ± SD	4.4 (0.4)	4.4 (0.4)	0.02	4.4 (0.4)	4.4 (0.4)	0.00
	Median (IQR)	4 (4-5)	4 (4-5)		4 (4-5)	4 (4-5)	
Baseline albumin-to-creatinine value, mg/g, No. (%)	No test	41,218 (67.3)	107,238 (68.5)	0.03	31,088 (67.4)	31,091 (67.4)	0.00
	Undetectable	5,832 (9.5)	12,254 (7.8)	0.06	4,340 (9.4)	4,408 (9.6)	0.01
	<30	9,790 (16.0)	22,006 (14.1)	0.05	7,284 (15.8)	7,343 (15.9)	0.00
	30-300	3,642 (5.9)	11,661 (7.4)	0.06	2,800 (6.1)	2,674 (5.8)	0.01
	>300	737 (1.2)	3,430 (2.2)	0.08	595 (1.3)	591 (1.3)	0.00
Prescriptions in the past 120 days, No. (%)							
Aspirin		1,549 (2.5)	2,532 (1.6)	0.06	1,018 (2.2)	959 (2.1)	0.01
Tylenol		2,939 (4.8)	2,879 (1.8)	0.17	1,664 (3.6)	1,473 (3.2)	0.02
Opiates		12,499 (20.4)	15,521 (9.9)	0.30	7,697 (16.7)	7,166 (15.5)	0.03
Angiotensin converting enzyme inhibitor		15,898 (26.0)	48,917 (31.2)	0.12	12,190 (26.4)	12,190 (26.4)	0.00
Angiotensin receptor blocker		16,618 (27.1)	37,556 (24.0)	0.07	12,139 (26.3)	12,139 (26.3)	0.00
Statin		32,296 (52.8)	84,994 (54.3)	0.03	24,343 (52.8)	24,269 (52.6)	0.00
Diabetes drug		13,159 (21.5)	37,247 (23.8)	0.05	10,097 (21.9)	10,087 (21.9)	0.00

Variable	Value	Baselines Pre-Match			Baselines Post-Match		
		NSAID users n=61,219	Non-users n=156,589	Stan. Diff.	NSAID users n=46,107	Non-users n=46,107	Stan. Diff.
Calcium channel blocker		16,386 (26.8)	45,357 (29.0)	0.05	12,400 (26.9)	12,244 (26.6)	0.01
Calcium channel blocker combination		782 (1.3)	1,867 (1.2)	0.01	587 (1.3)	576 (1.2)	0.01
Beta-blocker		14,136 (23.1)	48,987 (31.3)	0.19	10,921 (23.7)	11,045 (24.0)	0.01
Beta-blocker combination		305 (0.5)	398 (0.3)	0.03	201 (0.4)	181 (0.4)	0.00
Proton pump inhibitor		24,196 (39.5)	40,148 (25.6)	0.30	16,246 (35.2)	15,737 (34.1)	0.02
Thiazide diuretic		8,871 (14.5)	22,768 (14.5)	0.00	6,461 (14.0)	6,466 (14.0)	0.00
Loop diuretic		3,137 (5.1)	16,247 (10.4)	0.20	2,270 (4.9)	2,213 (4.8)	0.00
Potassium-sparing diuretic		1,877 (3.1)	6,000 (3.8)	0.04	1,251 (2.7)	1,230 (2.7)	0.00
Trimethoprim / sulfamethoxazole		854 (1.4)	2,564 (1.6)	0.02	633 (1.4)	630 (1.4)	0.00
Anti-psychotic		1,271 (2.1)	7,259 (4.6)	0.14	1,037 (2.2)	970 (2.1)	0.01
Antidepressant		10,426 (17.0)	26,895 (17.2)	0.01	7,504 (16.3)	7,450 (16.2)	0.00
Aliskiren		37 (0.1)	7 (0.0)	0.04	<5 (0.0)	<5 (0.0)	0.00
Potassium supplement		69 (0.1)	1,050 (0.7)	0.10	53 (0.1)	54 (0.1)	0.00
Antineoplastic		1,913 (3.1)	5,142 (3.3)	0.01	1,456 (3.2)	1,461 (3.2)	0.00
Anticonvulsent		4,131 (6.7)	7,948 (5.1)	0.07	2,846 (6.2)	2,621 (5.7)	0.02
Benzodiazapine		8,989 (14.7)	16,399 (10.5)	0.13	6,128 (13.3)	5,964 (12.9)	0.01
Picosalax		663 (1.1)	1,600 (1.0)	0.01	465 (1.0)	469 (1.0)	0.00

Abbreviations: ADG, Aggregated Diagnostic Group; eGFR, estimated glomerular filtration rate; IQR, interquartile range; LHIN, Local Health Integration Network; N/A, not applicable; NSAIDs, Non-steroidal anti-inflammatory drugs; Stan. Diff., standardized difference; SD, standard deviation.

SI conversion factors: To convert serum creatinine from mg/dL to µmol/L, multiply by 88.4; to convert serum potassium from mEq/L to mmol/L multiply by 1.0; to convert albumin-to-creatinine ratio from mg/g to mg/mmol multiply by 0.113.

[a]Missing rural status was categorized as not rural.

[b]Missing income quintile was imputed into the third quintile.

Supplemental Table 8. Beta coefficients and odds ratios for significant predictors of 30-day acute kidney injury or hyperkalemia among NSAID users

Variable	Beta coefficient (95% CI)	Odds ratios (95% CI)
Intercept	-6.02 (-7.38, -4.67)	N/A
Age	0.013 (0.0011, 0.024)	1.01 (1.00, 1.02)
Sex (male versus female)	0.36 (0.21, 0.51)	1.44 (1.23, 1.67)
Baseline eGFR	-0.036 (-0.041, -0.031)	0.96 (0.96, 0.97)
Baseline serum potassium	0.58 (0.41, 0.76)	1.79 (1.50, 2.14)
ACEi or ARB prescription	0.21 (0.051, 0.37)	1.24 (1.05, 1.45)
Any diuretic prescription versus none	0.57 (0.42, 0.73)	1.76 (1.49, 2.08)

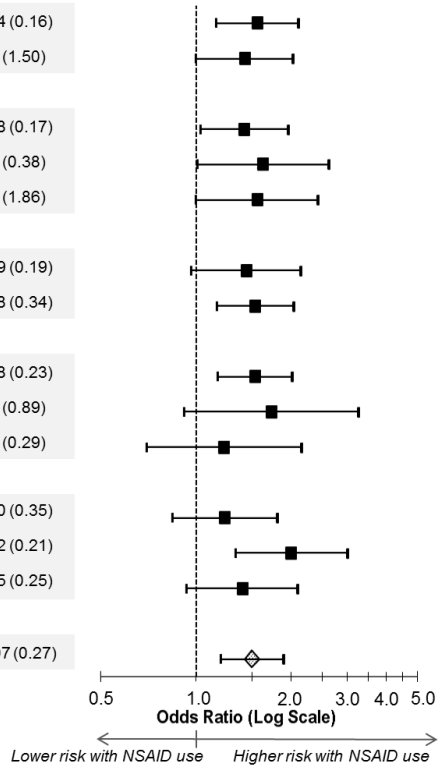
Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; eGFR, estimated glomerular filtration rate; N/A, not applicable.

Supplemental Table 9. Clinical utility of prediction model based on different predicted risk thresholds: number and proportion of patients captured by each threshold and the associated sensitivity, specificity, positive predictive value, and negative predictive value

Predicted risk threshold	>1%	>5%	>10%
Patients at risk based on cut-point, No. (%)	22,187 (36.2)	1207 (1.97)	111 (0.18)
Sensitivity, % (95% CI)	67.8 (64.3-71.4)	14.0 (11.4-16.6)	2.6 (1.4-3.7)
Specificity, % (95% CI)	64.1 (63.7-64.5)	98.2 (98.1-98.3)	99.8 (99.8-99.9)
Positive Predictive Value, % (95% CI)	2.1 (2.0-2.3)	8.1 (6.6-9.7)	16.2 (9.4-23.3)
Negative Predictive Value, % (95% CI)	99.4 (99.3-100)	99.0 (98.9-99.1)	98.9 (98.8-99.0)

Supplemental Figure 1. Sub-group analyses for the outcome of hyperkalemia from prescription NSAID use

Subgroup	*Events/Total patients at risk (%)*		*Odds Ratio (95% CI)*	*P-value for interaction*
	NSAID users	**Non-users**		
Baseline potassium (mEq/L)				
<5	109/42,564 (0.26)	70/42,564 (0.16)	1.57 (1.16-2.12)	0.7
5-5.5	75/3543 (2.12)	53/3543 (1.50)	1.42 (1.00-2.03)	
Baseline eGFR (mL/min/1.73 m²)				
60+	88/36,208 (0.24)	62/36,208 (0.17)	1.42 (1.03-1.96)	
45-<60	44/7096 (0.62)	27/7096 (0.38)	1.63 (1.01-2.63)	0.9
<45	52/2803 (1.86)	34/2803 (1.86)	1.56 (1.00-2.44)	
Baseline ACEi or ARB use				
None	60/21,969 (0.27)	42/21,969 (0.19)	1.44 (0.97-2.14)	0.8
ACEi / ARB	124/24,138 (0.51)	81/24,138 (0.34)	1.54 (1.16-2.04)	
Baseline diuretic use				
None	130/36,728 (0.35)	85/36,728 (0.23)	1.54 (1.17-2.02)	
Thiazide or loop	27/1797 (1.50)	16/1797 (0.89)	1.73 (0.92-3.27)	0.7
K-sparing	27/7582 (0.36)	22/7582 (0.29)	1.23 (0.70-2.16)	
% of maximum NSAID dose[a]				
<50%	58/13,440 (0.43)	47/13,440 (0.35)	1.23 (0.84-1.81)	
50<80%	68/16,142 (0.42)	34/16,142 (0.21)	2.00 (1.33-3.02)	0.9
75%+	58/16,525 (0.35)	42/16,525 (0.25)	1.40 (0.93-2.10)	
Overall				
	184/46,107 (0.40)	123/46,107 (0.27)	1.50 (1.20-1.89)	N/A

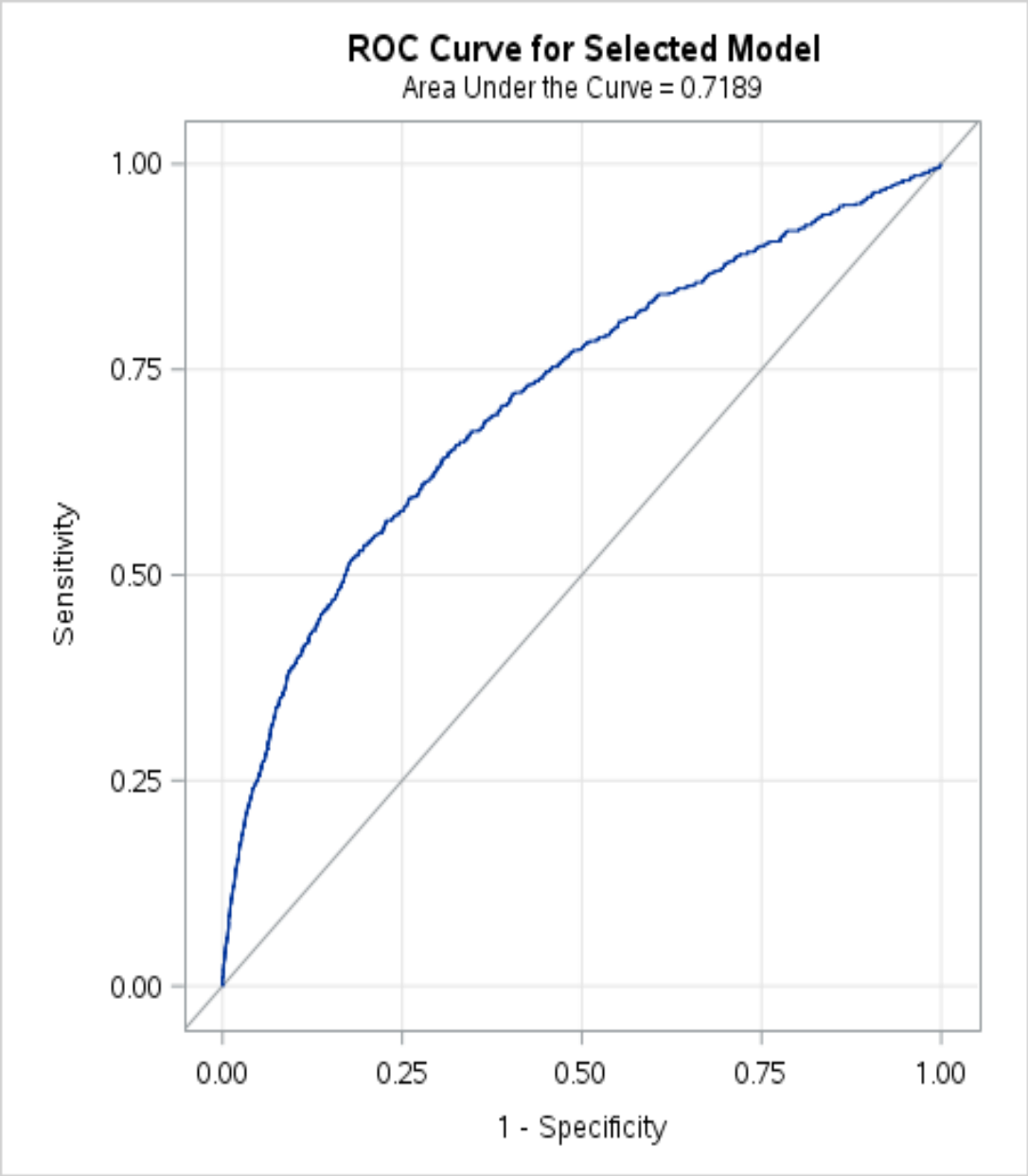


Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; eGFR, estimated glomerular filtration rate; N/A, not applicable; NSAIDs, non-steroidal anti-inflammatory drugs.

SI conversion factor: To convert serum potassium from mEq/L to mmol/L multiply by 1.0.

[a]We defined percentage of maximum NSAID daily dose by the NSAID group, with the non-user group following their matched NSAID user.

Supplemental Figure 2. Receiver operating characteristic curve for the prediction model of acute kidney injury or hyperkalemia risk



Supplemental Methods 1. Description of methodology used to identify proportion of older adults receiving an NSAID prescription in Ontario, Canada

Denominator:

1) We identified all patients 65 years or older who were alive between April 1, 2006 and March 31, 2015.

Numerator:

1) Using the Ontario Drug Benefits database, we identified all patients from the denominator with at least one prescription for an NSAID (using same drug names from main study) between April 1, 2006 and March 31, 2015.
2) We restricted to one prescription per person to identify number of unique people.

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5. STUDY 4

Title: Routine laboratory monitoring after starting angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers and the association with clinical outcomes: a population-based cohort study

Running title: Outcomes of ACEi or ARB laboratory monitoring

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5.1 ABSTRACT

Objective: To evaluate the association between receipt of outpatient laboratory serum creatinine and potassium monitoring after angiotensin converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) initiation and clinical outcomes.

Design: Two population-based retrospective cohort studies.

Setting: Kaiser Permanente Northern California (KPNC), United States, and Ontario, Canada; 2007 to 2015.

Participants: Patients with both outpatient serum creatinine and potassium tests in the 30 days after starting ACEi or ARB therapy (54,274 from KPNC and 59,520 from Ontario), compared to 1:1 matched patients without follow-up testing who had similar indicators of baseline health status.

Main outcome measures: The primary outcome was 30-day all-cause mortality. Secondary outcomes included 30-day hospitalization with acute kidney injury or hyperkalemia. We used Cox proportional hazards regression stratified on matched pairs. Results from the two cohorts were meta-analyzed using a random effects model if heterogeneity was low (I^2 <75%).

Results: Follow-up testing compared to no testing was not significantly associated with all-cause mortality: 0.16% versus 0.20%, adjusted hazard ratio (HR) 0.70 (95% confidence interval [CI] 0.46 to 1.06) for KPNC and 0.24% versus 0.19%, adjusted HR 1.20 (95% CI 0.86 to 1.66) for Ontario. Follow-up testing compared to no testing was significantly associated with higher rates of hospitalization with acute kidney injury

(0.24% versus 0.12%, pooled HR 1.96, 95% CI 1.49 to 2.58), and hyperkalemia (0.06% versus 0.03%, pooled HR 1.88, 95% CI 1.04 to 3.11).

Conclusions: There was no difference in 30-day mortality for patients receiving routine laboratory monitoring after ACEi or ARB initiation compared to those without such monitoring.

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5.2 BACKGROUND

Renin-angiotensin-aldosterone system (RAAS) blockade therapy is used for the primary treatment of hypertension (i.e. angiotensin converting enzyme inhibitors [ACEi] or angiotensin II receptor blockers [ARB] medications), as well as to preserve kidney function for patients with or at risk for chronic kidney disease [1]. Initiating ACEi or ARB prescriptions can cause acute kidney injury or hyperkalemia [2–5], which may increase the risk of subsequent cardiovascular events, kidney failure, and death [6–11].

Ordering routine laboratory tests to monitor serum creatinine and potassium levels shortly after initiating RAAS blockade therapy may allow providers to identify laboratory concerns early and intervene to prevent serious complications. Consensus-based clinical practice guidelines recommend this routine practice for all patients but especially for higher-risk patients such as those with chronic kidney disease [12–16] (Supplementary Table 1). However, these recommendations are based on evidence that ACEi and ARBs can cause acute kidney injury and hyperkalemia, and there is a lack of evidence that laboratory monitoring itself prevents adverse clinical outcomes [17,18]. It is unlikely a randomized clinical trial will be done to establish the utility of laboratory monitoring after ACEi or ARB initiation, since clinical practice guideline recommendations for this practice already exist. Furthermore, practice patterns for routine monitoring after initiating RAAS blockade therapy may differ across North America. For these reasons, we completed two population-based cohort studies in two different North American regions to determine if routine laboratory monitoring versus no routine monitoring after ACEi or ARB initiation is associated with a lower risk of 30-day all-cause mortality,

hospitalization with acute kidney injury, and hospitalization with hyperkalemia. We also identified significant predictors of receiving laboratory monitoring within 30 days after initiating ACEi or ARB therapy.

5.3 METHODS

Research Design

We conducted two retrospective cohort studies using electronic health record data from Kaiser Permanente Northern California (KPNC), United States and population-based data from Ontario, Canada. We followed reporting guidelines for observational studies (Supplementary Table 2) [19].

Research Setting and Data Sources

Kaiser Permanente Northern California (KPNC) is a large integrated healthcare delivery system caring for >4.4 million members in the San Francisco and greater Bay Area. Its membership has broad age, gender, racial/ethnic and comorbidity diversity, and is highly representative of the local and statewide population [20]. Comprehensive electronic health record data that is standardized and linked at the patient-level are available through the KPNC Virtual Data Warehouse, including data on demographics, vital status, outpatient prescriptions, laboratory tests, and healthcare encounters across both outpatient and inpatient settings [21,22]. All analyses for this cohort were conducted at KPNC in Oakland, California, United States. This study was approved by the KPNC institutional review board.

The province of Ontario, Canada has more than 13 million residents, 17% of whom are 65 years or older [23]. Healthcare services in Ontario are funded through the Ontario Health Insurance Plan program; with the exception of outpatient medications, which are only funded for segments of the population, including all people 65 years and older [24]. These healthcare encounters are recorded in administrative databases, which are linked using unique, encoded identifiers and held at ICES. The use of ICES data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a Research Ethics Board. See Supplementary Table 3 for a description of Ontario, Canada datasets used for this study.

Cohort Assembly and Exposure Categorization

We identified patients who received an ACEi or ARB prescription between January 1, 2007 and December 31, 2015. For the KPNC cohort, we included all patients 18 years of age or older. For the Ontario cohort, we only included patients 66 years of age or older, excluding those in their first year of prescription drug coverage (between age 65 and 66 years) to ensure complete medication history.

We excluded the following patients from both cohorts: 1) those who received an ACEi or ARB prescription in the previous 180 days, to ensure new users, 2) those with both an ACEi and ARB on the prescription date, since co-prescription increases risk of adverse outcomes, 3) those without at least one outpatient value for both serum creatinine and serum potassium in the prior year to assess baseline levels, 4) those with baseline potassium values >5.5 mEq/L or a prescription for a potassium binder in the previous 180

days, 5) baseline eGFR >150 mL/min/1.73 m^2, which is likely a data error, and 6) patients with a history of end-stage kidney disease (**Figure 1**).

For routine monitoring, patients typically receive a laboratory requisition for serum creatinine and electrolyte testing at the time of their initial ACEi or ARB prescription, where the blood sample is drawn in the following several weeks. We defined outpatient laboratory monitoring as serum creatinine and serum potassium test completion within one to 30 days following the ACEi or ARB prescription date. We selected first evidence of laboratory monitoring for each patient with at least one follow-up outpatient serum creatinine and potassium test and excluded patients if they did not have both tests done at the same time. We considered the date of testing the index date or the start date to follow patients for outcome ascertainment. We excluded patients who were classified as having died in the period between the prescription and index dates, as this was a data error. We also excluded patients if they had evidence of certain healthcare encounters (hospitalization, emergency department visit, any other laboratory tests completed, or visit with a primary care physician, nephrologist, internist, endocrinologist, or cardiologist) between the prescription date and day prior to index date, as this may have suggested that testing was done in response to new symptoms or an adverse event rather than routine monitoring.

To reduce potential bias in outcome ascertainment, we randomly assigned an index date (or a phantom test date) to patients in the non-test group based on the distribution of time between the prescription and index dates in the follow-up test group. For the non-test group, we repeated the exclusions described above. The reason we

excluded patients in the non-test group who died in the period between the prescription date and index date was to avoid the potential for immortal time bias, since patients in the test group (by definition) could not die during this period. See Supplementary Methods 1 for additional details, including minor differences in the creation of the KPNC and Ontario cohorts.

Outcomes

We assessed clinical outcomes on index date or in the following 30 days. We used a 30-day follow-up since clinically significant increases in serum creatinine and potassium following ACEi or ARB initiation generally present within this time period [25–27]. Our primary outcome was all-cause mortality. Our secondary outcomes were hospitalization with acute kidney injury and hospitalization with hyperkalemia. We chose these secondary outcomes since laboratory monitoring can identify an abnormality that is managed in an outpatient or emergency department setting, preventing the need for hospital admission. We defined acute kidney injury events based on the 2012 Kidney Disease Improving Global Outcomes (KDIGO) thresholds, which was a rise in serum creatinine of at least 50% or 0.3 mg/dL, compared to the baseline value [28]. We selected the highest serum creatinine value either within the first three days of a hospitalization or during an emergency department visit which resulted in a hospital admission. We identified hyperkalemia events using the highest serum potassium value within the first two days of a hospitalization or during an emergency department visit which resulted in

hospital admission. We defined hyperkalemia as a serum potassium value of at least 5.5 mEq/L.

Our two additional outcomes were all-cause hospitalization and hospital encounter (hospitalization or emergency department visit) with ventricular arrhythmia or sudden cardiac death. See Supplementary Methods 2 for further outcome details for the Ontario study. Among patients who received routine testing, we also described the rise in serum creatinine and potassium values from baseline. All outcomes were accurately coded in our data sources with the exception of hospital encounter with ventricular arrhythmia, which we expected to have limited sensitivity (see Supplementary Table 4 for coding definitions and validation).

Analysis

We conducted all analyses in KPNC using SAS version 9.3 and in Ontario using version 9.4 (SAS Institute, Cary, NC). We compared baseline characteristics for the test and non-test groups before and after matching using standardized differences [29]. Standardized differences of more than 10% were considered potentially meaningful [29].

As an additional analysis, we identified baseline characteristics that significantly predicted receipt of routine laboratory monitoring after ACEi or ARB initiation. We performed bootstrapping with replacement to generate 100 unique samples from each of our original cohorts and performed stepwise logistic regression analyses on each sample [30]. We used $P<0.05$ to identify variables both to enter and remain in the model. We flagged significant predictors as variables that were retained in at least 80% of the models

and ran a final logistic regression model with these variables to identify the odds ratios and 95% confidence intervals (CI) [30].

We used high-dimensional propensity scores to balance the two groups on indicators of baseline health. A high-dimensional approach describes a data mining algorithm to identify confounders (or proxies of true confounders) using healthcare data [31]. See Supplementary Table 5 for details on the high-dimensional propensity score methodology for both cohorts.

We matched patients in the routine monitoring group 1:1 to patients in the non-test group using greedy matching without replacement [32]. Matching criteria included baseline eGFR ±5 mL/min/1.73 m^2, baseline serum potassium ±0.5 mEq/L, age ±2 years, and high-dimensional propensity score ±0.2 standard deviations of the logit of the high-dimensional propensity score. We calculated estimated glomerular filtration rates (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [33].

We used Cox proportional hazards regression stratified on matched pairs to obtain hazard ratios (HR) and 95% CIs for the risk of our outcomes in the test versus non-test groups. We pooled the results from the two cohorts using a random effects model for the meta-analyses only when heterogeneity was not high (I^2 <75%) [34].

We also repeated analyses adjusting for pre-specified confounding variables, and any variables that were significantly different between the test and non-test groups after matching. The pre-specified confounding variables included sex (Ontario)/ gender (KPNC), index year, time from prescription date to index date, prescription drug class (ACEi, ACEi combination, ARB, ARB combination), prescription drug dose (percent of

maximal dose), concurrent or previous diuretic use, previous non-steroidal anti-inflammatory drug prescription, previous diagnosis of congestive heart failure, and previous diagnosis of peripheral vascular disease.

We performed *a priori* subgroup analyses for baseline kidney function (as patients with chronic kidney disease have a higher risk of acute kidney injury and hyperkalemia than patients without chronic kidney disease) [35,36], baseline serum potassium values (since patients with lower and higher baseline potassium levels compared to normal levels have a higher risk of death) [6,8,37,38], and age (to compare results for older adults from KPNC to the Ontario cohort).

In all analyses, a two-tailed $P<0.05$ was considered statistically significant. The only reason for loss to follow-up in the KPNC cohort occurred when patients disenrolled from the KPNC health plan (2.3% per year). KPNC data sources were complete for all variables except for self-reported race (20% missing), body mass index (45% missing), and systolic blood pressure (44% missing). The rate of emigration from Ontario is very low (0.1% per year) and is the only reason for lost follow-up in these data sources [39]. Ontario data sources were complete for all study variables except for ACEi or ARB prescriber data (15% missing), rural status (<0.01% missing), and income quintile (<0.5% missing).

Patient and Public Involvement

No patients were involved in the study design or interpretation of the results. Patients were not invited to contribute to the writing or editing of this manuscript.

5.4 RESULTS

Kaiser Permanente Northern California Cohort

Kaiser Permanente Northern California Cohort

We identified 164,254 eligible adults initiating ACEi or ARB therapy between 2007 and 2015 at KPNC (**Figure 1**), of which 55,487 (34%) received a routine outpatient serum creatinine and potassium test, a mean of 12 days after their ACEi or ARB prescription. The mean (SD) serum creatinine value in those with routine laboratory monitoring was 1.0 (0.4) mg/dL and 1704 (3.1%) of patients met the KDIGO threshold for acute kidney injury (Supplementary Table 6 & 7) [28]. We found 36 variables that significantly predicted whether patients received routine follow-up laboratory monitoring, including older age, the presence of heart failure, atrial fibrillation / flutter or higher blood pressure, the use of loop or thiazide diuretics, and lower baseline eGFR (Supplementary Table 8).

The final cohort included 54,274 eligible adults with follow-up tests matched to 54,274 without tests. Patients had a mean (SD) age of 63 (14) years and approximately 53% were women. After matching, there remained a significant difference in some characteristics including smoking, year of study entry, body mass index, blood pressure, ACEi or ARB dose, and time from baseline serum creatinine and potassium tests to prescription date (see **Table 1** for selected baseline characteristics and Supplementary Table 9 for full baseline table).

Primary outcome of all-cause mortality

See **Figure 2** for all outcomes. Overall, 193 patients (0.2%) died within 30 days. Follow-up testing versus no testing was not significantly associated with 30-day mortality: 85 (0.16%) versus 108 (0.20%), HR 0.78, 95% CI 0.59-1.03. Results were similar in fully-adjusted analysis (adjusted HR 0.70, 95% CI 0.46-1.06) (**Figure 2**). In addition, baseline kidney function, baseline serum potassium, and age did not significantly modify the association between routine follow-up testing versus no testing and all-cause mortality (all interaction $P>0.2$; **Figure 3**).

Secondary outcomes of hospitalization with acute kidney injury and hyperkalemia

Overall, 145 patients (0.1%) were hospitalized with acute kidney injury within 30 days (0.08% were KDIGO stage one). Follow-up testing versus no testing was significantly associated with a higher risk of hospitalization with acute kidney injury: 93 (0.17%) versus 52 (0.09%), HR 1.82, 95% CI 1.30-2.57. This association persisted in adjusted analyses (HR 2.44, 95% CI 1.40-4.26) (**Figure 2**). Meta-analysis of the unadjusted outcome for the two cohorts was also significant (pooled HR 1.96, 95% CI 1.49-2.58, $I^2=0\%$). The association between follow-up testing and hospitalization with acute kidney injury in KPNC was not significantly modified by baseline kidney function, baseline serum potassium, or age (interaction $P>0.5$; Supplementary Figure 1).

Overall, 33 patients (0.03%) were hospitalized with hyperkalemia within 30 days. Follow-up testing versus no testing was not significantly associated with the risk of hospitalization with hyperkalemia in the KPNC cohort: 22 (0.04%) versus 11 (0.02%), HR 2.00, 95% CI 0.97-4.12 (**Figure 2**). Meta-analysis of the outcome for the two cohorts

showed that follow-up testing versus no testing was significantly associated with a higher risk of hospitalization with hyperkalemia (pooled HR 1.80, 95% CI 1.04-3.11, I^2=0%).

Additional outcomes

Follow-up testing versus no testing was not significantly associated with sudden cardiac death or hospital encounter with ventricular arrhythmia. Follow-up testing versus no testing was significantly associated with a higher risk of all-cause hospitalization. This association was significantly modified by baseline kidney function, serum potassium, and age (all interaction P<0.05; Supplementary Figure 2). For instance, the association was higher for patients without baseline chronic kidney disease (HR 2.19, 95% CI 1.95-2.45) compared to those with a baseline eGFR <45 mL/min/1.73 m^2 (HR 1.74, 95% CI 1.32-2.29) (interaction P=0.04).

Ontario Cohort

We initially identified 278,183 patients with an ACEi or ARB prescription between 2007 and 2015, of which 60,277 (22%) received serum creatinine and potassium monitoring (Supplementary Figure 3). The final Ontario cohort included 59,520 patients with follow-up tests matched to 59,520 without tests. Patients had a mean (SD) age of 75 (7) years and approximately 53% were women. Among those with routine laboratory monitoring, 1790 (3.0%) patients met the KDIGO threshold for acute kidney injury (Supplementary Table 6 & 7) (28).

Compared to patients in the KPNC cohort, patients in the Ontario cohort were older and generally had greater comorbidity, lower baseline eGFR, and similar baseline serum potassium (**Table 1** and Supplementary Table 10). Many of these differences persisted when we compared the Ontario cohort to patients aged 66 years and older in the KPNC cohort (Supplementary Table 11).

Overall, 255 patients in Ontario (0.2%) died within 30 days. Follow-up testing versus no testing in the adjusted analysis was not associated with 30-day all-cause mortality (HR 1.20, 95% CI 0.86-1.66). Results were consistent with those observed in the KPNC cohort for other outcomes (**Figure 2**).

5.5 DISCUSSION

In large population-based cohorts from two different North American regions, we found that routine laboratory monitoring after ACEi or ARB initiation was not associated with lower rates of all-cause mortality. However, routine laboratory monitoring was associated with higher rates of hospitalizations (for any reason, with acute kidney injury, or with hyperkalemia) likely due to abnormalities detected with testing.

Two previous retrospective cohort studies on this topic reported conflicting results [17,18]. McDowell et al. (2010) looked at the association between monitoring of serum creatinine, potassium, sodium, or urea after initiating an antihypertensive medication and adverse outcomes including drug discontinuation, hospitalization, or death. Similar to our study results, these authors found no significant differences in death rates between patients who received monitoring and patients who did not; however, patients who

received monitoring were more likely to be hospitalized and to discontinue their medication [18]. Raebel et al. (2010) assessed the association between serum potassium monitoring after initiation of an ACEi, ARB or spironolactone and hyperkalemia-associated outcomes among adults with diabetes [17]. In contrast to our findings, these authors found that potassium monitoring had a protective association for hyperkalemia-associated events (composite of hospitalization or emergency department visit with hyperkalemia or hyperkalemia-related death) [17]. However, an emergency department visit for a clinically high serum potassium value soon after routine testing could be a positive outcome if the physician who identified the test result advised their patient to go to the emergency department to prevent downstream outcomes such as hospitalization or death.

We identified many demographic characteristics, health care utilization and comorbidities that were associated with receiving laboratory monitoring among both cohorts. Different factors were identified as predictors in KPNC compared to Ontario, demonstrating the diversity of our populations.

We completed subgroup analyses to identify if certain patient groups initiating an ACEi or ARB would benefit more from monitoring. In contrast to recommendations from clinical guidelines [12–15,40], we found that patients with chronic kidney disease at baseline did not appear to have better outcomes with monitoring compared to patients with no monitoring. However, given the small number of events for most of our outcomes, the estimates are imprecise and should be interpreted cautiously. We showed that there was a stronger association between monitoring and all-cause hospitalization for

patients with higher eGFR at baseline compared to those with lower eGFR. This is likely because healthcare providers may be more concerned when patients who are generally healthy receive abnormal test results, compared to patients who already have reduced kidney function.

Researchers in Sweden and the U.S. have developed and validated a model to predict hyperkalemia events within one year after initiating an ACEi or ARB, which showed good discrimination and calibration in both internal and external validation cohorts [41]. They found that risk factors for hyperkalemia after ACEi or ARB initiation included male gender, diabetes, congestive heart failure, use of potassium-sparing diuretics, lower baseline eGFR, and higher baseline serum potassium [41]. Prediction models can be used in clinical practice to help healthcare providers identify which patients would benefit most from routine ACEi or ARB monitoring.

Strengths and Limitations

We demonstrated consistent results using data from two different North American regions, providing greater confidence in the observed associations. We used high-dimensional propensity scores to balance the testing and non-testing groups on important indicators of baseline health [31,42,43], a method that appears to control for confounding more effectively than standard adjustment methods by systematically evaluating a wide range of healthcare data [44–46]. However, despite using rigorous methods to account for confounding, there is still risk of residual confounding in all observational studies. In our data, we could not capture patients who received laboratory requisitions at the time of

ACEi or ARB initiation and never completed the testing; adherence with healthcare recommendations may be associated with better outcomes. We aimed to reduce concerns that the outpatient tests were done in response to patient symptoms or illness (referred to as confounding by indication) by excluding patients who had healthcare encounters between the prescription and test dates. However, residual confounding by indication may explain the observed association between testing and a higher risk of hospitalization. It is also possible laboratory abnormalities identified from testing led to a detailed medical review that prompted subsequent hospitalization. We did not examine follow-up care patterns for patients with an abnormal test result, since our data did not allow us to examine all interactions between providers and patients, including phone calls or emails. Also, we cannot make any conclusions on reasons for possible care gaps; for example, we would not know if providers recommended patients to seek follow-up care but patients were non-adherent.

Conclusion

Overall, we found no difference in 30-day mortality for patients receiving routine laboratory monitoring after ACEi or ARB initiation compared to those without such monitoring.

What is already known on this topic

- Clinical practice guidelines recommend routine serum creatinine and potassium monitoring shortly after initiating an angiotensin converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB).
- There is a lack of evidence that laboratory monitoring prevents adverse clinical outcomes.

What this study adds

- Our study suggests that routine laboratory monitoring after ACEi or ARB initiation may not prevent adverse outcomes.

Ethics Approval and Consent to Participate

This study was approved by the Kaiser Permanente Northern California institutional review board.

ICES is a prescribed entity under section 45 of Ontario's Personal Health Information Protection Act. Section 45 authorizes ICES to collect personal health information, without consent, for the purpose of analysis or compiling statistical information with respect to the management of, evaluation or monitoring of, the allocation of resources to or planning for all or part of the health system. Projects conducted under section 45, by definition, do not require review by a Research Ethics Board. This project was conducted under section 45 and approved by ICES' Privacy and Compliance Office.

Transparency Statement

The lead authors affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Author Contributions

DMN, AXG and ASG developed the initial study plan. RVP, SB, MMR, EM, TCT, FKR, MS, and GEN provided input and approved of the study and analysis plan. RVP completed all analyses for KPNC and DMN completed all analyses for Ontario with the assistance of EM. All authors interpreted the results. DMN drafted the initial manuscript, and all other authors critically reviewed and revised the manuscript. All authors read and approved the final manuscript.

Declaration of Conflicting Interests

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Consent for Publication

Not applicable.

Data Sharing

Data sets from Kaiser Permanente Northern California are not available to be accessed.

The data set from the Ontario study is held securely in coded form at ICES. While data sharing agreements prohibit ICES from making the data set publicly available,

access can be granted to those who meet pre-specified criteria for confidential access, available at www.ices.on.ca/DAS.

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5.7 TABLES & FIGURES

Table 1. Selected baseline characteristics for matched patients initiating angiotensin converting enzyme inhibitors or angiotensin receptor blockers, January 1, 2007 - December 31, 2015

Variable	KPNC Cohort			Ontario Cohort		
	Follow-up tests (N=54,274)	No follow-up tests (N=54,274)	Stan. Diff.	Follow-up tests (N=59,520)	No follow-up tests (N=59,520)	Stan. Diff.
Demographic characteristics						
Age, mean (SD), year	63.0 (13.6)	63.0 (13.6)	<1%	75.5 (6.9)	75.4 (6.9)	<1%
Women, No. (%)	28,842 (53.1)	28,653 (52.8)	1%	31,166 (52.4)	31,593 (53.1)	1%
Self-reported Race, No. (%)						
White	30,427 (56.1)	30,083 (55.4)	1%	N/A	N/A	
Black/African American	4102 (7.6)	4218 (7.8)	1%	N/A	N/A	
Asian/Pacific Islander	9284 (17.1)	9091 (16.8)	1%	N/A	N/A	
Other/Unknown	10,461 (19.3)	10,882 (20.1)	2%	N/A	N/A	
Hispanic ethnicity, No. (%)	7533 (13.9)	7838 (14.4)	1%	N/A	N/A	
Household income <$35,000/year, No. (%)	2965 (5.5)	3405 (6.3)	3%	N/A	N/A	
Income quintile, No. (%)*						
1 (lowest)	N/A	N/A		10,988 (18.5)	11,024 (18.5)	<1%
2	N/A	N/A		12,347 (20.7)	12,358 (20.8)	<1%
3	N/A	N/A		11,955 (20.1)	11,882 (20.0)	<1%
4	N/A	N/A		12,255 (20.6)	12,230 (20.5)	<1%
5 (highest)	N/A	N/A		11,975 (20.1)	12,026 (20.2)	<1%
Rural residence, No. (%)†	N/A	N/A		8409 (14.1)	8303 (13.9)	1%
Time from prescription date to index date, mean (SD), days	11.8 (7.0)	11.5 (7.1)	4%	11.3 (8.3)	12.4 (8.5)	**13%**
Year of prescription date, No. (%)						
2007	13,887 (25.6)	17,154 (31.6)	**13%**	52 (0.1)	87 (0.1)	<1%
2008	7819 (14.4)	6728 (12.4)	6%	1836 (3.1)	2268 (3.8)	4%
2009	6172 (11.4)	5046 (9.3)	7%	5423 (9.1)	5202 (8.7)	1%
2010	5001 (9.2)	4759 (8.8)	1%	7763 (13.0)	7471 (12.6)	1%
2011	5085 (9.4)	4335 (8.0)	5%	8129 (13.7)	7529 (12.6)	3%
2012	4550 (8.4)	4197 (7.7)	3%	9159 (15.4)	9953 (16.7)	4%
2013	5077 (9.4)	4758 (8.8)	2%	9395 (15.8)	8889 (14.9)	2%
2014	3636 (6.7)	3902 (7.2)	2%	10,116 (17.0)	9198 (15.5)	4%
2015	3047 (5.6)	3395 (6.3)	3%	7647 (12.8)	8923 (15.0)	6%
Medical history in the 5 years prior to or on prescription date (unless otherwise specified), No. (%)						
Johns Hopkins ADG	N/A	N/A		7.8 (3.8)	7.8 (3.8)	1%

Variable	KPNC Cohort			Ontario Cohort		
	Follow-up tests (N=54,274)	**No follow-up tests (N=54,274)**	**Stan. Diff.**	**Follow-up tests (N=59,520)**	**No follow-up tests (N=59,520)**	**Stan. Diff.**
score in the 2 years prior to or on prescription date, mean (SD)						
Charlson comorbidity score						
0 or no hospitalization	N/A	N/A		40,942 (68.8)	41,092 (69.0)	<1%
1	N/A	N/A		7376 (12.4)	7507 (12.6)	1%
2	N/A	N/A		5615 (9.4)	5587 (9.4)	<1%
3 or more	N/A	N/A		5587 (9.4)	5334 (9.0)	1%
Heart failure	2535 (4.7)	2038 (3.8)	4%	7833 (13.2)	7686 (12.9)	1%
Peripheral arterial disease	315 (0.6)	299 (0.6)	<1%	943 (1.6)	957 (1.6)	<1%
Diabetes mellitus	10,844 (20.0)	10,347 (19.1)	2%	24,893 (41.8)	25,083 (42.1)	1%
Hypertension	43,148 (79.5)	41,927 (77.3)	5%	50,053 (84.1)	50,318 (84.5)	1%
Dyslipidemia	32,779 (60.4)	32,296 (59.5)	2%	19,296 (32.4)	19,199 (32.3)	<1%
Cancer	2646 (4.9)	2195 (4.0)	4%	8567 (14.4)	7966 (13.4)	3%
Dementia	749 (1.4)	898 (1.7)	2%	5514 (9.3)	5371 (9.0)	1%
Smoking status						
Current Smoker	2362 (4.4)	2186 (4.0)	2%	N/A	N/A	
Former smoker	10,619 (19.6)	8079 (14.9)	**12%**	N/A	N/A	
Non-smoker	41,293 (76.1)	44,009 (81.1)	**12%**	N/A	N/A	
Body mass index category in the one year prior to or on prescription date, No. (%), kg/m^2						
<18.5	310 (0.6)	224 (0.4)	3%	N/A	N/A	
18.5-<25	7589 (14.0)	5727 (10.6)	10%	N/A	N/A	
25-<30	12,085 (22.3)	9401 (17.3)	13%	N/A	N/A	
30-<40	11,509 (21.2)	10,101 (18.6)	7%	N/A	N/A	
≥40	1491 (2.7)	1288 (2.4)	2%	N/A	N/A	
Unknown	21,290 (39.2)	27,533 (50.7)	**23%**	N/A	N/A	
Systolic blood pressure category in the one year prior to or on prescription date, No. (%), mmHg						
<120	4412 (8.1)	4217 (7.8)	1%	N/A	N/A	
120-<130	4712 (8.7)	4365 (8.0)	3%	N/A	N/A	
130-<140	8489 (15.6)	7443 (13.7)	5%	N/A	N/A	
140-<160	12,584 (23.2)	8926 (16.4)	**17%**	N/A	N/A	
160-<180	2959 (5.5)	2086 (3.8)	8%	N/A	N/A	
≥180	532 (1.0)	386 (0.7)	3%	N/A	N/A	
Unknown	20,586 (37.9)	26,851 (49.5)	**24%**	N/A	N/A	
ACE inhibitor or ARB prescription characteristics						
Prescription class, No. (%)						
ACE inhibitor	32,447 (59.8)	32,964 (60.7)	2%	35,573 (59.8)	33,089 (55.6)	9%
ACE inhibitor / thiazide combination	15,776 (29.1)	14,750 (27.2)	4%	3074 (5.2)	3339 (5.6)	2%
ARB	5680 (10.5)	6128 (11.3)	3%	16,642 (28.0)	18,025 (30.3)	5%
ARB / thiazide combination	371 (0.7)	432 (0.8)	1%	4231 (7.1)	5067 (8.5)	5%
Percentage of	26.6 (17.8)	31.2 (23.2)	**22%**	51.5 (28.6)	55.5 (29.8)	**14%**

Variable	KPNC Cohort			Ontario Cohort		
	Follow-up tests (N=54,274)	**No follow-up tests (N=54,274)**	**Stan. Diff.**	**Follow-up tests (N=59,520)**	**No follow-up tests (N=59,520)**	**Stan. Diff.**
maximum daily dose, mean (SD)						
Baseline medication use in the 120 days prior to or on prescription date, n (%)						
Beta blocker	17,503 (32.2)	16,553 (30.5)	4%	18,163 (30.5)	17,839 (30.0)	1%
Calcium channel blocker	7339 (13.5)	6989 (12.9)	2%	17,865 (30.0)	17,988 (30.2)	<1%
Loop diuretic	3385 (6.2)	3096 (5.7)	2%	7,269 (12.2)	6,153 (10.3)	6%
Thiazide diuretic	19,150 (35.3)	18,203 (33.5)	4%	18,538 (31.1)	18,809 (31.6)	1%
Potassium-sparing diuretic	362 (0.7)	368 (0.7)	<1%	3,053 (5.1)	2,464 (4.1)	5%
Any anti-hypertensive agent	34,342 (63.3)	33,194 (61.2)	4%	40,638 (68.3)	40,250 (67.6)	2%
Statin	22,175 (40.9)	21,619 (39.8)	2%	32,706 (54.9)	32,903 (55.3)	1%
NSAID	7992 (14.7)	7782 (14.3)	1%	6268 (10.5)	6909 (11.6)	4%
Diabetic therapy	5661 (10.4)	6062 (11.2)	3%	15,299 (25.7)	15,712 (26.4)	2%
Baseline laboratory values in the one year prior to or on prescription date						
eGFR, No. (%), mL/min/1.73 m^2						
60-150	44,370 (81.8)	44,387 (81.8)	<1%	40,955 (68.8)	40,955 (68.8)	<1%
45-<60	6816 (12.6)	6808 (12.5)	<1%	11,059 (18.6)	11,059 (18.6)	<1%
30-<45	2577 (4.7)	2568 (4.7)	<1%	5750 (9.7)	5782 (9.7)	<1%
15-<30	499 (0.9)	502 (0.9)	<1%	1675 (2.8)	1653 (2.8)	<1%
<15	12 (0.0)	9 (0.0)	<1%	81 (0.1)	71 (0.1)	<1%
Serum creatinine, mean (SD), mg/dL	0.9 (0.3)	0.9 (0.3)	<1%	1.0 (0.4)	1.0 (0.4)	<1%
Time from baseline serum creatinine to prescription date, median (IQR), days	69 (13-186)	41 (6-144)	**21%**	104 (28-223)	69 (19-181)	**26%**
Serum potassium, No. (%), mEq/L						
<5.0	51,433 (94.8)	51,433 (94.8)	<1%	54,440 (91.5)	54,440 (91.5)	<1%
5.0-5.5	2841 (5.2)	2841 (5.2)	<1%	5080 (8.5)	5080 (8.5)	<1%
Time from baseline potassium to prescription date, median (IQR), days	79 (14-201)	50 (7-161)	**21%**	114 (31-232)	80 (22-197)	**23%**
Baseline healthcare utilization in the one year prior to or on prescription date						
Primary care visits, mean (SD)	4.7 (5.3)	4.3 (4.5)	8%	8.8 (9.0)	8.6 (8.4)	3%
Hospitalizations, mean (SD)	0.2 (0.6)	0.2 (0.6)	5%	0.2 (0.6)	0.2 (0.6)	3%
Emergency department visits, mean (SD)	0.4 (0.9)	0.4 (0.9)	3%	0.7 (1.3)	0.6 (1.3)	3%
Nephrology visits, mean (SD)	0.0 (0.4)	0.0 (0.3)	4%	0.2 (1.0)	0.2 (0.9)	2%
Prescribing physician characteristics						
Physician age, mean	N/A	N/A		53.2 (10.5)	54.9 (10.4)	**17%**

Variable	KPNC Cohort			Ontario Cohort		
	Follow-up tests (N=54,274)	**No follow-up tests (N=54,274)**	**Stan. Diff.**	**Follow-up tests (N=59,520)**	**No follow-up tests (N=59,520)**	**Stan. Diff.**
(SD), years						
Unknown, n (%)	N/A	N/A		9986 (16.8)	8698 (14.6)	6%
Physician specialty, No. (%)						
Nephrologist	N/A	N/A		1365 (2.3)	993 (1.7)	4%
Primary care	N/A	N/A		40,250 (67.6)	42,624 (71.6)	9%
Cardiologist	N/A	N/A		3916 (6.6)	3300 (5.5)	5%
Other	N/A	N/A		4003 (6.7)	3907 (6.6)	<1%
Unknown	N/A	N/A		9986 (16.8)	8696 (14.6)	6%
Time since graduation, years, mean (SD)	N/A	N/A		26.9 (10.9)	28.6 (10.8)	**16%**
Unknown, n (%)	N/A	N/A		9986 (16.8)	8701 (14.6)	6%

Abbreviations: ACE, angiotensin converting enzyme; ADG, Aggregated Diagnostic Groups; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; KPNC, Kaiser Permanente Northern California; IQR, interquartile range; NSAID, non-steroidal anti-inflammatory drug; SD, standard deviation; Stan. Diff., standardized difference.

* Missing imputed into the middle (third) income quintile.

† Missing categorized as not rural

Figure 1. Cohort assembly for patients in the Kaiser Permanente Northern California study, January 1, 2007 - December 31, 2015

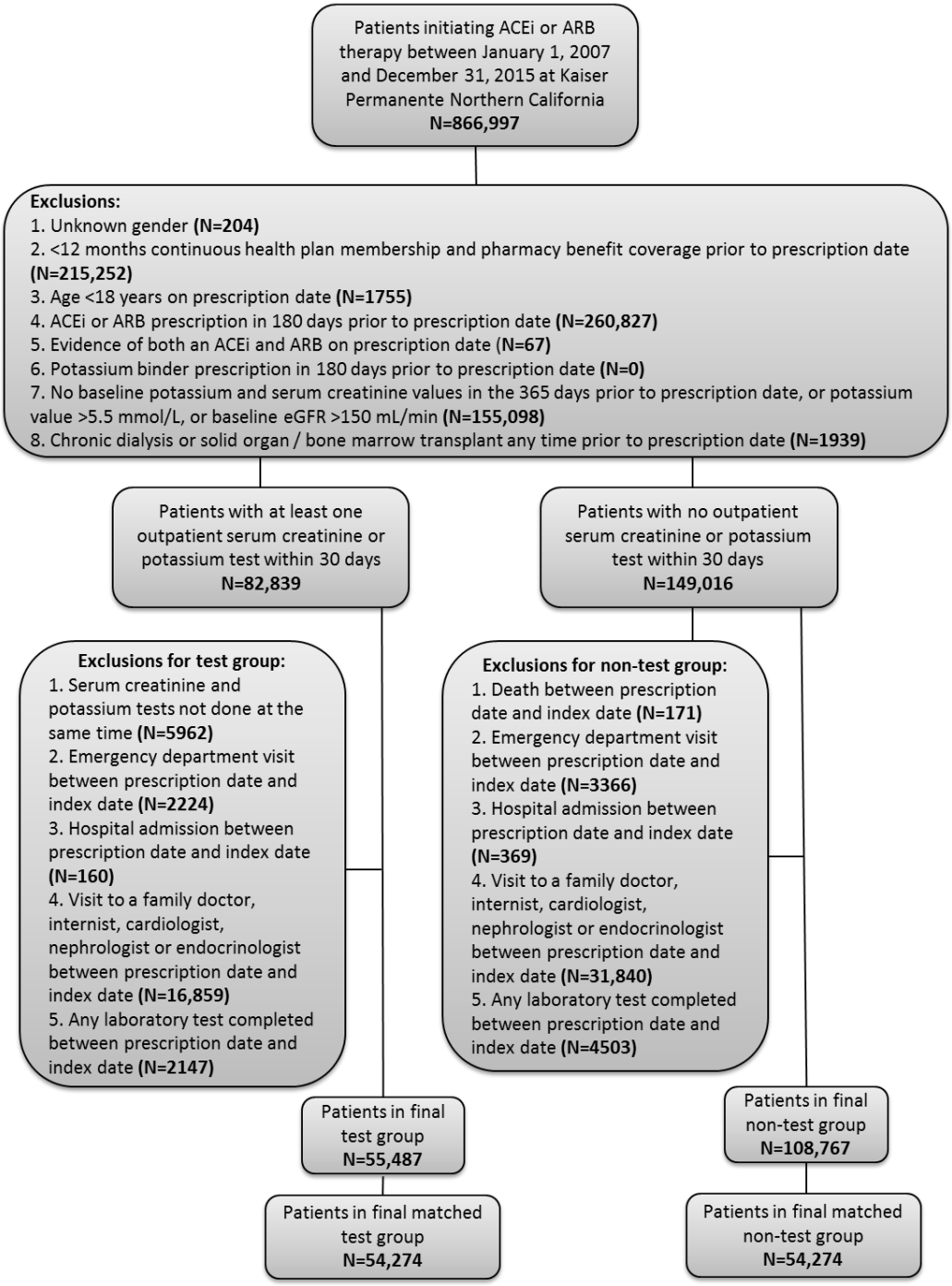
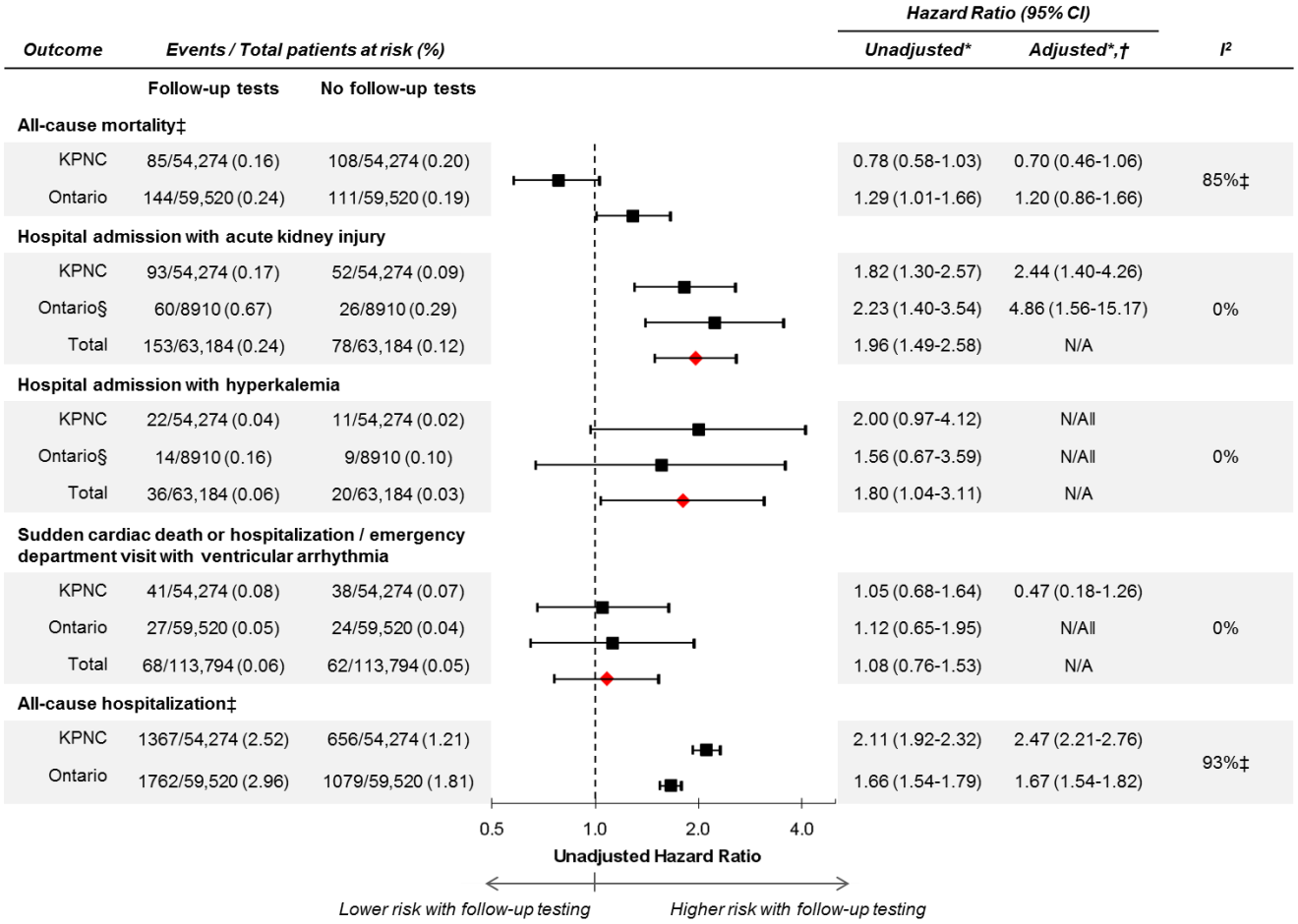


Figure 2. Primary and secondary outcomes comparing high-dimensional propensity score-matched patients who received routine follow-up serum creatinine and potassium tests after ACEi or ARB initiation to patients who did not receive follow-up tests



Abbreviations: CI, confidence interval; KPNC, Kaiser Permanente Northern California; N/A, not available.

* KPNC analyses were matched on age, baseline eGFR, baseline potassium, and high-dimensional propensity score. Ontario analyses were matched on age, baseline eGFR, baseline potassium, high-dimensional propensity score, and patients residing in the Ontario laboratory catchment area.

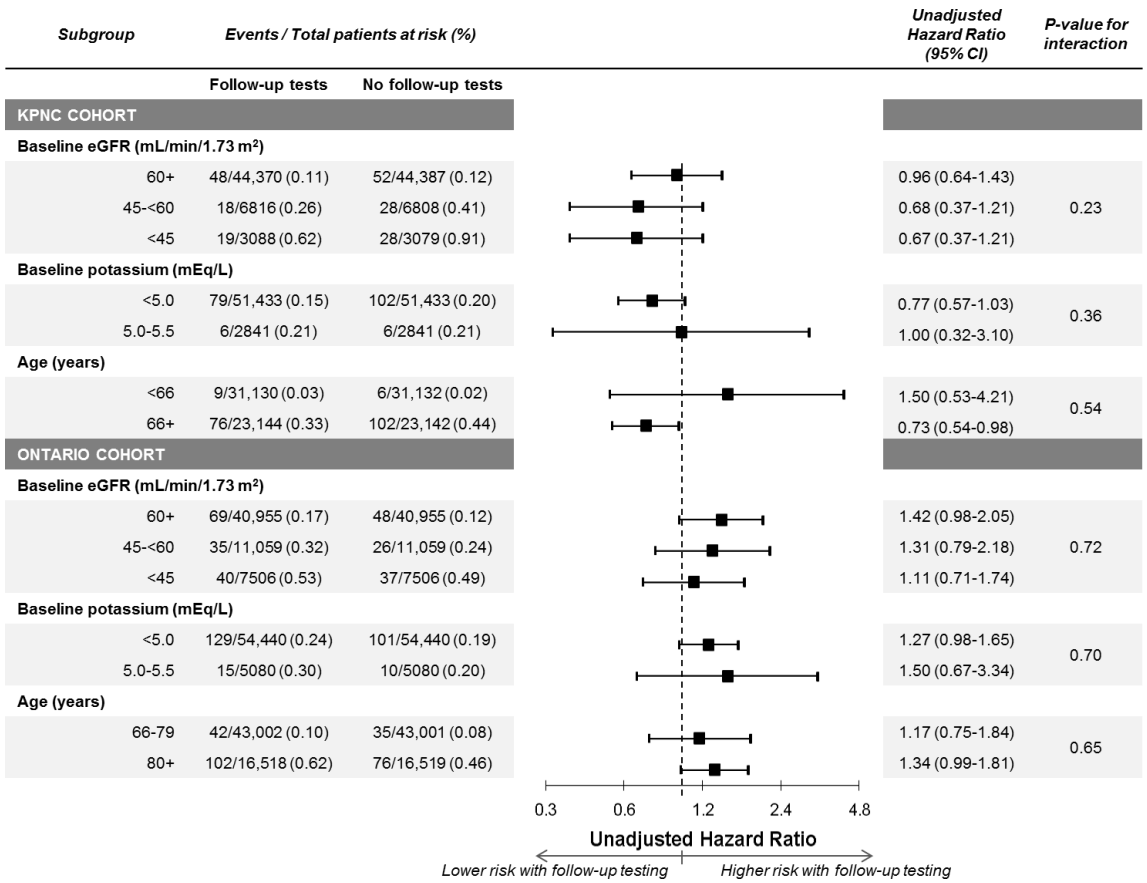
† KPNC analyses were adjusted for gender, prescription date, prescription class, prescription dose, peripheral arterial disease, congestive heart failure, previous diuretic prescription, previous non-steroidal anti-inflammatory drug, smoking status, year of study entry, body mass index, blood pressure, time from baseline serum creatinine to prescription date, and time from baseline serum potassium to prescription date. Ontario analyses were adjusted for gender, prescription date, prescription class, prescription dose, peripheral arterial disease, congestive heart failure, previous diuretic prescription, previous non-steroidal anti-inflammatory drug, time from baseline serum creatinine to prescription date, time from baseline serum potassium to prescription date, prescribing physician age, and prescribing physician time since graduation.

‡ Combined results not shown due to significant heterogeneity (I^2 >75%).

§ Outcomes only among the 8910 patients who resided in the Ontario laboratories catchment area (see Appendix Methods 2 for details).

|| Adjusted result not shown, since models would not converge.

Figure 3. Subgroup analyses for the outcome of all-cause mortality comparing high-dimensional propensity score-matched patients who received routine follow-up serum creatinine and potassium tests after ACEi or ARB initiation to patients who did not receive follow-up tests



Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; KPNC, Kaiser Permanente Northern California.

5.8 APPENDICES

Appendix Table 1. Clinical guidelines recommending laboratory test monitoring after initiating an ACEi or ARB

Appendix Table 2. Checklist of recommendations for reporting of observational studies using the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement

Appendix Table 3. Data sources available at the ICES and used for the Ontario study

Appendix Table 4. Administrative codes used to define outcomes

Appendix Table 5. High-dimensional propensity score methodology for KPNC and Ontario studies

Appendix Table 6. Descriptive characteristics of the test results among patients who received follow-up serum creatinine and potassium tests

Appendix Table 7. Descriptive characteristics of the test results among patients who received follow-up serum creatinine and potassium tests stratified by baseline estimated glomerular filtration rate, baseline serum potassium, and age

Appendix Table 8. Predictors of receiving follow-up serum creatinine and potassium testing among KPNC and Ontario cohorts

Appendix Table 9. All baseline characteristics for Kaiser Permanente Northern California cohort before and after matching, January 1, 2007 – December 31, 2015

Appendix Table 10. All baseline characteristics for Ontario cohort before and after matching, January 1, 2007 – December 31, 2015

Appendix Table 11. Baseline characteristics for patients >66 years of age in the KPNC cohort

Appendix Table 12. Baseline characteristics for patients in the Ontario laboratory catchment area (Ontario cohort only)

Appendix Figure 1. Subgroup analyses for the outcome of hospitalization with acute kidney injury comparing patients who received follow-up serum creatinine and potassium tests to propensity-matched patients without follow-up tests

Appendix Figure 2. Subgroup analyses for the outcome of all-cause hospitalization comparing patients who received follow-up serum creatinine and potassium tests to propensity-matched patients without follow-up tests

Appendix Figure 3. Cohort assembly for patients in the Ontario study

Appendix Methods 1. Differences between the KPNC and Ontario cohort assembly

Appendix Methods 2. Laboratory outcome assessment across Ontario hospitals

Appendix Table 1. Clinical guidelines recommending laboratory test monitoring after initiating an ACEi or ARB

Condition/ Setting	Reference/ Guideline	Recommendation
Kidney disease	KDIGO 2013[1]	"Assess GFR and measure serum potassium within 1 week of starting or following any dose escalation." Note: this is not part of the main recommendations and is only included in a table about cautionary notes for prescribing in patients with CKD.
Kidney disease	K/DOQI 2004[2]	"Patients treated with ACE inhibitors or ARBs should be monitored for hypotension, decreased GFR, and hyperkalemia. (A)*" "In most patients, the ACE inhibitor or ARB can be continued if: a GFR decline over 4 months is <30% from baseline value or serum potassium is ≤5.5 mEq/L."†
Kidney disease	Ontario Renal Network 2015[3]	A serum creatinine and potassium test should be done within 2 weeks after initiation of ACEi or ARB.
Kidney disease	National Institute for Health and Clinical Excellence (NICE) 2014[4]	Among patients with chronic kidney disease, serum potassium and creatinine should be measured within 1 to 2 weeks after initiating an ACEi or ARB, and after any dose increase. Based on this serum creatinine measurement, if the eGFR decreases by 25% or greater, or the serum creatinine increases by 30% or greater then: - Identify if there are any other potential causes for a decline in kidney function, such as volume depletion or concurrent medication (e.g., NSAIDs) - If no other cause for decline in kidney function is identified then stop the ACEi or ARB prescription or reduce the dose to a previously tolerated dose, and prescribe an additional antihypertensive medication if needed
Primary care	NHS, Specialist Pharmacy Service 2017[5]	"CKS advise monitoring renal function and serum electrolytes 1–2 weeks after starting treatment and 1–2 weeks after each dose increase. If eGFR falls by 25% or more or plasma creatinine increases by 30% or more from baseline, stop the ACEi/ARB or reduce to a previously tolerated dose once potential alternative causes of renal impairment have been ruled out. If the changes indicating a decrease in renal function are less than described do not modify the dose but repeat the test in 1-2 weeks." References NICE's 2014 CKD

		guidelines
Primary care (heart failure and hypertension)	Smellie 2006[6]	Among patients with heart failure: serum creatinine and electrolytes should be measured in the 1-2 weeks after each dose increase/ relevant drug addition in low-risk patients, and 5-7 days after initiating treatment for high-risk patients (including CKD). Among patients with hypertension, serum creatinine and electrolytes should be measured at 1 week after initiating treatment, and 4-10 days after initiating treatment for high-risk patients (including CKD).
Hypertension	Hypertension Canada (CHEP) 2016[7]	Although the guidelines mention the risk of hyperkalemia for patients on ACEi or ARBs, they do not include any recommendations or statements on lab monitoring except for patients with non-diabetic chronic kidney disease and proteinuria: "Carefully monitor renal function and potassium for those on an ACE inhibitor or ARB."
Hypertension	British Columbia Ministry of Health Services 2016[8]	Monitor serum creatinine and potassium at initiation of ACEi or ARB therapy and periodically thereafter.
Diabetes	American Diabetes Association 2018[9]	"For patients treated with an ACE inhibitor, angiotensin receptor blocker, or diuretic, serum creatinine/estimated glomerular filtration rate and serum potassium levels should be monitored at least annually."‡ This recommendation is particularly relevant for patients with reduced kidney function, since they are at an increased risk of developing acute kidney injury and hyperkalemia. (Not graded)
Diabetes	Canadian Diabetes Association 2013[10]	Serum creatinine and potassium should be checked within 1-2 weeks of initiation of ACEi or ARB, or dose titration. "If potassium becomes elevated or creatinine increases by more than 30% from baseline, therapy should be reviewed and serum creatinine and potassium levels should be rechecked."
Heart disease	American College of Cardiology/ American Heart Association Task Force on Clinical Practice Guidelines 2017[11]	"Monitoring of serum sodium and potassium levels is helpful during diuretic or RAS blocker titration, as are serum creatinine and urinary albumin as markers of CKD progression." Note: this is not part of the main recommendations.

Monitoring for adverse drug reactions for antihypertensive treatment	McDowell 2013[12]	- 18 guidelines for monitoring serum creatinine and 17 for serum potassium. - Guidelines rarely referenced primary research to support the recommendations. - Overall recommendation was to check serum creatinine and potassium at 4 and 10 days following treatment initiation in high-risk patients including those with chronic kidney disease, or check within 2 weeks if not high risk.
Hyperkalemia	Palmer 2004[13]	"Measure potassium 1 week after initiating therapy or after increasing dose of drug. If potassium increases to ≤5.5 mmol/liter, decrease dose of drug; if patient is taking some combination of an ACE inhibitor, an angiotensin-receptor blocker, and an aldosterone-receptor blocker, discontinue one and recheck potassium. If potassium is >5.5 mmol/liter despite steps described above, discontinue drugs."
Medication use in elderly	Knight 2001[14]	"If a vulnerable elder begins receiving an ACE inhibitor, then serum potassium and creatinine levels should be checked within 1 week of initiation of therapy."

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CHEP, Hypertension Canada; CKD, chronic kidney disease; CKS, clinical knowledge summaries; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease Improving Global Outcomes; K/DOQI, Kidney Disease Outcomes Quality Initiative; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NSAID, non-steroidal anti-inflammatory drug; RAS, renin-angiotensin system.

* Strong Recommendation/ Evidence.

† It is recommend that clinicians follow the guideline; moderately strong evidence that the behavior improves outcomes.

‡ Supportive evidence from well-conducted cohort studies.

Appendix Table 2. Checklist of recommendations for reporting of observational studies using the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement [15]

	Item No	STROBE items	RECORD items	Reported
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract. (b) Provide in the abstract an informative and balanced summary of what was done and what was found.	(1.1) The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. (1.2) If applicable, the geographic region and time frame within which the study took place should be reported in the title or abstract. (1.3) If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Title and Abstract
Introduction				
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported.		Background
Objectives	3	State specific objectives, including any prespecified hypotheses.		Background
Methods				
Study design	4	Present key elements of study design early in the paper.		Methods – Research Design
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection.		Methods – Research Setting and Data Sources
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. (b) For matched studies, give matching criteria and number of exposed and unexposed.	(6.1) The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. (6.2) Any validation studies of the codes or algorithms used to select the population should be referenced. If	Methods – Cohort Assembly and Exposure Categorization

			validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. (6.3) If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	(7.1) A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Methods – Outcomes & Analysis; Appendix Table 4
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group.		Methods – Research Setting and Data Sources; Appendix Table 3
Bias	9	Describe any efforts to address potential sources of bias.		Methods – Analysis
Study size	10	Explain how the study size was arrived at.		N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why.		Methods – Analysis
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding. (b) Describe any methods used to examine subgroups and interactions. (c) Explain how missing data were addressed. (d) If applicable, explain how loss to follow-up was addressed. (e) Describe any sensitivity analyses.		Methods – Analysis

Data access and cleaning methods		N/A	(12.1) Authors should describe the extent to which the investigators had access to the database population used to create the study population. (12.2) Authors should provide information on the data cleaning methods used in the study.	Methods – Analysis
Linkage		N/A	(12.3) State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	Methods – Research Setting and Data Sources
Results				
Participants	13	(a) Report numbers of individuals at each stage of study--e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed. (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram.	(13.1) Describe in detail the selection of the persons included in the study (i.e., study population selection), including filtering based on data quality, data availability, and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Results; Figure 1; Appendix Figure 3
Descriptive data	14	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders. (b) Indicate number of participants with missing data for each variable of interest. (c) Summarize follow-up time (e.g. average and total amount).		Results; Table 1; Appendix Table 6 & 7
Outcome data	15	Report numbers of outcome events or summary measures over time.		Results; Figure 2
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g. 95% confidence interval). Make clear which confounders were adjusted for and why they were included. (b) Report category boundaries when continuous variables		Results; Figure 2

		were categorized. (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period.		
Other analyses	17	Report other analyses done (e.g. analyses of subgroups and interactions, and sensitivity analyses).		Results; Figure 3; Appendix Figures 1 & 2
Key results	18	Summarize key results with reference to study objectives.		Discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	(19.1) Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Discussion – Strengths and limitations
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.		Discussion
Generalizability	21	Discuss the generalizability (external validity) of the study results.		Discussion
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based.		Funding Declaration
Accessibility of protocol, raw data, and programming code		N/A	(22.1) Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Availability of Data and Materials

Appendix Table 3. Data sources available at ICES and used for the Ontario study

Database	Description	Use in Study
Ontario Drug Benefit	This database contains highly accurate records of all dispensed outpatient prescriptions covered through the Ontario Drug Benefit program.(53)	• ACEi / ARB prescriptions for study inclusion • Baseline prescription drug use
Ontario Laboratories Information System	Database contains laboratory test orders and results from hospitals, community laboratories, and public health laboratories.	• Laboratory test values for serum creatinine, potassium, hemoglobin, and albumin/creatinine ratio values at baseline • Serum creatinine values to estimate GFR* • Follow-up serum creatinine and potassium values to identify exposure group and secondary outcomes of acute kidney injury and hyperkalemia
Canadian Institute for Health Information's Discharge Abstract Database / Same Day Surgery	This database contains diagnostic and procedural information for all hospitalizations and same day surgeries. We used the 10th edition of the Canadian Modified International Classification of Disease system (ICD-10) to define comorbidities and the Canadian Classification for Health Interventions (CCI) to define healthcare procedures.	• Baseline comorbidities and number of previous hospitalizations • Previous receipt of dialysis or transplant for cohort exclusions • Outcomes for hospitalization with acute kidney injury, hyperkalemia, ventricular arrhythmia and all cause hospitalization
National Ambulatory Care Reporting System	Database contains information on hospital and community based ambulatory care (i.e. emergency department) visits. We used the 10th edition of the Canadian Modified International Classification of Disease system (ICD-10) to define comorbidities and the Canadian Classification for Health Interventions (CCI) to define healthcare procedures.	• Baseline comorbidities and number of previous emergency department visits
Ontario Health Insurance Plan	Database includes diagnostic information, and health claims for inpatient and outpatient services.	• Baseline primary care physician / nephrologist visits (past year), preventative health care procedures, and comorbidities • Previous receipt of dialysis or transplant for cohort exclusions
ICES Physician Database†	Database contains physician related information such as birth date, gender, education, and medical specializations.	• Prescribing physician characteristics • Previous visits to primary care physician / nephrologist at baseline
Registered Persons Database‡	Database contains information on patient demographics including gender, birth and death dates.	• Baseline demographics • Death date for outcome of all-cause mortality

Office of the Registrar General-Deaths	Database contains information on all registered deaths including the cause of death.	• Cause of death for cardiac death outcome
Client Agency Program Enrollment	Database contains information on program enrolment with specific practitioners and groups.	• Baseline primary care reimbursement (program) type
Johns Hopkins Ambulatory Clinical Groups (ACG®) System Version 10.0 [17]	Software uses existing patient data to model as well as predict healthcare utilization.	• Baseline comorbidity

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; GFR, glomerular filtration rate.

* In order to estimate estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology (CKD-EPI) equation, we assumed all patients to be non-black since we did not have information on race and less than 5% of the Ontario population is of black race [18].

† Some missing data for patients in our cohort for ACEi / ARB prescribing physicians (missing for approximately 15% of patients).

‡ Some missing data for patients in our cohort included rural status (<0.005% missing) and income quintile (<0.5% missing).

Appendix Table 4. Administrative codes used to define outcomes

Outcome	Data Sources	Definition	Codes	Validity
All-cause mortality	Ontario: RPDB KPNC: Electronic health records, member proxy reporting, Social Security Administration files, and California death certificate information	Evidence of death date in the 30 days following index date	Ontario: N/A KPNC: N/A	Ontario: Sensitivity of 97.8%; Specificity of 100%(56) KPNC: N/A
Hospitalization with acute kidney injury	Ontario: CIHI-DAD, OLIS KPNC: KPNC Virtual Data Warehouse	Evidence of hospital admission in the 30 days following the index date with at least one serum creatinine lab value with ≥50% increase in serum creatinine or ≥0.3 mg/dL or greater from baseline value.	Ontario: LOINC code to identify serum creatinine lab test value: 14682-9 KPNC: LOINC code to identify serum creatinine lab test value 2160-0	Laboratory values are the gold standard when compared to administrative coding algorithms.
Hospitalization with hyperkalemia	Ontario: CIHI-DAD, OLIS KPNC: KPNC Virtual Data Warehouse	Evidence of hospital admission in the 30 days following the index date with at least one serum potassium lab value ≥5.5 mEq/L.	Ontario: at least one LOINC code to identify potassium lab test values: 2823-3, 6298-4, 39789-3 KPNC: LOINC code to identify potassium lab test values: 2823-3	Laboratory values are the gold standard when compared to administrative coding algorithms.
All-cause hospitalization	Ontario: CIHI-DAD KPNC: KPNC Virtual Data	Evidence of hospital admission in the 30 days following the	Ontario: N/A KPNC: N/A	Ontario: 99% agreement between original coder and

	Warehouse	index date		reabstractor KPNC: N/A
Hospital encounter with ventricular arrhythmia or sudden cardiac death	Ontario: CIHI-DAD, NACRS, ORGD KPNC: KPNC Virtual Data Warehouse	Ontario: Evidence of one of the specified ICD-10 codes for ventricular arrhythmia in CIHI-DAD or NACRS or one of the following cardiac cause of death codes in ORGD. KPNC: Evidence of ICD-9 or ICD-10 code for ventricular arrhythmia, or ICD-10 code for underlying cause of cardiac death	Ontario: Ventricular arrhythmia: I4900, I472 Cardiac death: 410, 411, 412, 413, 414, 4296, 4297, 428, 435, 3623, 4349, 436, 430, 431, 432, 4340, 4341, 426, 427, 7850, 394, 395, 396, 3970, 3971, 4240, 4241, 4242, 4243, 401, 402, 404, 405, 4249, 425, 4291, 4292, 4293, 4294, 4295, 4298, 4299, 433, 437, 438, 440, 441, 442, 4431, 44381, 44389, 4439, 444, 9960, V533, V450 KPNC: Ventricular arrhythmia: ICD9: 427.4, 427.41, 427.42, 427.1 ICD10: I49.0, I49.01, I49.02, I47.0, I47.1, I47.2 Cardiac death: I11, I11.0, I11.9, I20, I20.0, I20.1, I20.8, I20.9, I21, I21.0, I21.1, I21.2, I21.3, I21.4, I21.9, I22, I22.0, I22.1, I22.2, I22.8, I22.9, I23, I23.0, I23.1, I23.2, I23.3, I23.4, I23.5, I23.6, I23.7, I23.8, I24, I24.0, I24.1, I24.8, I24.9, I25, I25.1, I25.2, I25.3, I25.4, I25.5, I25.6, I25.7, I25.8, I25.9	Ontario: Positive predictive value of 92%(57) KPNC: N/A

Abbreviations: CIHI, Canadian Institute for Health Information; DAD, Discharge Abstract Database; ICD-10, International Classification of Diseases 10th edition; KPNC, Kaiser Permanente Northern California; LOINC, Logical Observation Identifiers Names and Codes; N/A, not available; NACRS, National Ambulatory Care Reporting System; OLIS, Ontario Laboratory Information System; ORGD, Ontario Registrar General; RPDB, Registered Persons Database.

Appendix Table 5. High-dimensional propensity score methodology for KPNC and Ontario studies

Methodology / model characteristics	KPNC	Ontario
Look-back period	4 years	4 years
Data sources	1) Admission diagnoses in the inpatient, outpatient, and emergency department settings, 2) Procedures in the inpatient, outpatient, and emergency department settings, 3) Drug names for outpatient medications	1) The most responsible diagnosis and main intervention codes for hospital and same day surgery data, 2) The most responsible diagnosis and main intervention codes for emergency department data, 3) Physician billing codes for diagnoses and interventions, 4) Drug names for outpatient medications
Top N most prevalent variables selected from each data source	250	100
Number of variables retained for the final propensity score	400	500
Demographic variables forced into the model in addition to retained variables	Age, gender, race, and Hispanic ethnicity	Age, gender, rural status, income quintile, and local health integration network

Appendix Table 6. Descriptive characteristics of the test results among patients who received follow-up serum creatinine and potassium tests

	High serum creatinine*	Acute kidney injury stage 2 or more†	Serum potassium ≥5.5 mEq/L	Serum potassium ≥6.0 mEq/L	Serum potassium ≥6.5 mEq/L
KPNC Cohort					
No. (%)	1704 (3.1)	101 (0.2)	519 (0.9)	63 (0.1)	9 (0.0)
Ontario Cohort					
No. (%)	1790 (3.0)	67 (0.1)	1034 (1.7)	145 (0.2)	30 (0.1)

* Based on KDIGO definition for acute kidney injury: >50% increase or absolute increase of 0.3 mg/dL from baseline.

† A serum creatinine increase of >100% from baseline.

Appendix Table 7. Descriptive characteristics of the test results among patients who received follow-up serum creatinine and potassium tests stratified by baseline estimated glomerular filtration rate, baseline serum potassium, and age

Subgroup	Serum potassium at prescription date (mEq/L)				Serum creatinine at prescription date (mg/dL)				
	Value, mean (SD)	Absolute difference*, mean (SD)	Absolute difference*, median (IQR)	Value ≥5.5, n (%)	Value, mean (SD)	Absolute difference*, mean (SD)	Absolute difference*, median (IQR)	Relative difference*, mean (SD)	High serum creatinine†, n (%)
KPNC Cohort									
Overall	4.4 (0.4)	0.07 (0.4)	0.1 (-0.2, 0.3)	519 (0.9)	1.0 (0.4)	0.02 (0.2)	0.01 (-0.05, 0.08)	1.02 (0.2)	1704 (3.1)
Baseline eGFR									
60+	4.4 (0.4)	0.06 (0.4)	0.1 (-0.2, 0.3)	297 (0.7)	0.9 (0.2)	0.02 (0.1)	0.01 (-0.04, 0.08)	1.03 (0.2)	936 (2.1)
45-<60	4.4 (0.4)	0.1 (0.4)	0.1 (-0.2, 0.4)	114 (1.6)	1.2 (0.3)	0.01 (0.2)	-0.01 (-0.10, 0.09)	1.01 (0.2)	362 (5.1)
<45	4.5 (0.5)	0.13 (0.5)	0.1 (-0.2, 0.4)	108 (3.1)	1.7 (0.7)	0.01 (0.4)	-0.02 (-0.16, 0.14)	1.00 (0.2)	406 (11.6)
Baseline serum potassium									
<5	4.4 (0.4)	0.1 (0.4)	0.1 (-0.2, 0.3)	358 (0.7)	1.0 (0.3)	0.02 (0.2)	0.01 (-0.05, 0.08)	1.03 (0.2)	1565 (3.0)
5-5.5	4.8 (0.4)	-0.4 (0.4)	-0.4 (-0.6, -0.1)	161 (5.3)	1.1 (0.4)	0.02 (0.2)	0.01 (-0.06, 0.08)	1.02 (0.2)	139 (4.6)
Age									
<66	4.3 (0.4)	0.06 (0.4)	0.1 (-0.2, 0.3)	211 (0.7)	0.9 (0.3)	0.02 (0.2)	0.01 (-0.05, 0.07)	1.02 (0.2)	680 (2.2)
66+	4.4 (0.4)	0.09 (0.4)	0.1 (-0.2, 0.3)	308 (1.3)	1.0 (0.4)	0.03 (0.2)	0.01 (-0.05, 0.09)	1.03 (0.2)	1024 (4.3)
Ontario Cohort									
Overall	4.4 (0.4)	0.06 (0.4)	0.0 (-0.2, 0.3)	1034 (1.7)	1.0 (0.4)	0.02 (0.2)	0.01 (-0.06, 0.08)	0.03 (0.2)	1790 (3.0)
Baseline eGFR									
60+	4.4 (0.4)	0.05 (0.4)	0.0 (-0.2, 0.3)	493 (1.2)	0.9 (0.2)	0.02 (0.1)	0.01 (-0.03, 0.07)	0.03 (0.1)	572 (1.4)
45-<60	4.4 (0.5)	0.06 (0.4)	0.1 (-0.2, 0.3)	215 (1.9)	1.2 (0.2)	0.01 (0.2)	0.0 (-0.09, 0.08)	0.01 (0.2)	432 (3.9)
<45	4.6 (0.5)	0.1 (0.5)	0.1 (-0.2, 0.4)	326 (4.3)	1.7 (0.6)	0.02 (0.3)	0.0 (-0.1, 0.1)	0.01 (0.2)	798 (10.6)
Baseline serum potassium									
<5	4.4 (0.4)	0.09 (0.4)	0.1 (-0.2, 0.3)	566 (1.0)	1.0 (0.4)	0.02 (0.2)	0.01 (-0.5, 0.08)	0.03 (0.2)	1579 (2.9)
5-5.5	4.8 (0.5)	-0.3 (0.5)	-0.3 (-0.6, 0.0)	468 (9.2)	1.2 (0.5)	0.01 (0.2)	0.0 (-0.08, 0.08)	0.01 (0.2)	223 (4.4)
Age									
66-<80	4.4 (0.4)	0.05 (0.4)	0.0 (-0.2, 0.3)	729 (1.7)	1.0 (0.4)	0.02 (0.2)	0.01 (-0.05, 0.07)	0.02 (0.2)	1052 (2.5)
80+	4.4 (0.5)	0.07 (0.4)	0.1 (-0.2, 0.3)	305 (1.9)	1.1 (0.4)	0.02 (0.2)	0.01 (-0.06, 0.09)	0.03 (0.2)	750 (4.5)

Abbreviations: eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; KPNC, Kaiser Permanente Northern California; SD, standard deviation.

* Compared to most recent baseline values in the one year prior.

† Based on KDIGO definition for acute kidney injury: >50% increase or absolute increase of 0.3 mg/dL (26.5 µmol/L) from baseline.

Appendix Table 8. Predictors of receiving follow-up serum creatinine and potassium testing among KPNC and Ontario cohorts

Predictor Variable	Predictor Class	KPNC Cohort		Ontario Cohort	
		Repetition %	Odds Ratio (95% CI)	Repetition %	Odds Ratio (95% CI)
Age, years	18-39	100	Reference	N/A	N/A
	40-65	100	1.21 (1.15-1.27)	N/A	N/A
	66-74	100	1.43 (1.35-1.50)	100	Reference
	75-84	100	1.35 (1.27-1.43)	100	1.09 (1.07-1.11)
	>85	100	1.20 (1.11-1.29)	100	1.06 (1.03-1.10)
Women		99	1.07 (1.04-1.10)	99	1.00 (0.97-1.02)
Self-reported race	White	100	Reference	N/A	N/A
	Black/African American	100	0.74 (0.71-0.77)	N/A	N/A
	Asian/Pacific Islander	100	1.03 (1.00-1.06)	N/A	N/A
	Other/Unknown	100	0.88 (0.86-0.91)	N/A	N/A
Household income <$35,000/year		97	0.89 (0.85-0.93)	N/A	N/A
Patient rural status		N/A	N/A	82	1.08 (1.05-1.11)
Local Health Integration Network	1	N/A	N/A	100	Reference
	2	N/A	N/A	100	1.71 (1.60-1.82)
	3	N/A	N/A	100	1.87 (1.75-2.00)
	4	N/A	N/A	100	1.37 (1.29-1.46)
	5	N/A	N/A	100	1.51 (1.41-1.61)
	6	N/A	N/A	100	1.46 (1.37-1.56)
	7	N/A	N/A	100	1.37 (1.28-1.46)
	8	N/A	N/A	100	1.43 (1.34-1.52)
	9	N/A	N/A	100	1.49 (1.41-1.59)
	10	N/A	N/A	100	1.69 (1.58-1.82)
	11	N/A	N/A	100	1.39 (1.31-1.49)
	12	N/A	N/A	100	1.62 (1.51-1.75)
	13	N/A	N/A	100	1.40 (1.30-1.50)
	14	N/A	N/A	100	1.49 (1.35-1.64)
Time from index date to lab test		<80	N/A	100	0.99 (0.98-0.99)
Year of prescription date	2007	<80	N/A	100	0.56 (0.41-0.75)
	2008	<80	N/A	100	0.84 (0.79-0.89)
	2009	<80	N/A	100	1.02 (0.98-1.06)
	2010	<80	N/A	100	1.07 (1.03-1.11)
	2011	<80	N/A	100	1.12 (1.08-1.16)

Predictor Variable	Predictor Class	KPNC Cohort		Ontario Cohort	
		Repetition %	Odds Ratio (95% CI)	Repetition %	Odds Ratio (95% CI)
	2012	<80	N/A	100	1.10 (1.06-1.14)
	2013	<80	N/A	100	1.25 (1.21-1.29)
	2014	<80	N/A	100	1.34 (1.30-1.39)
	2015	<80	N/A	100	Reference
Johns Hopkins ADG score		N/A	N/A	100	1.01 (1.01-1.02)
Charlson comorbidity score		N/A	N/A	98	1.02 (1.01-1.03)
Acute myocardial infarction		<80	N/A	100	0.82 (0.77-0.86)
Heart failure		100	1.40 (1.31-1.49)	<80	N/A
Ischemic stroke or transient ischemic attack		80	0.89 (0.82-0.97)	<80	N/A
Mitral and/or aortic valvular disease		100	1.25 (1.17-1.34)	<80	N/A
Atrial flutter or fibrillation		100	1.43 (1.35-1.51)	94	1.09 (1.04-1.13)
Venous thromboembolism		83	1.30 (1.11-1.53)	<80	N/A
Percutaneous coronary intervention		91	1.17 (1.08-1.25)	<80	N/A
Diabetes		100	0.82 (0.79-0.85)	100	1.10 (1.07-1.13)
Hypertension		100	1.14 (1.11-1.17)	99	0.94 (0.92-0.97)
Dyslipidemia		99	0.91 (0.89-0.94)	<80	N/A
Hypothyroidism		<80	N/A	100	1.08 (1.05-1.12)
Cancer		<80	N/A	100	1.14 (1.11-1.18)
Cirrhosis		<80	N/A	100	1.29 (1.16-1.42)
Chronic lung disease		99	0.95 (0.92-0.98)	<80	N/A
Dementia		100	0.76 (0.69-0.84)	<80	N/A
Depression		100	0.87 (0.84-0.91)	<80	N/A
Smoking status	Non-smoker	100	Reference	N/A	N/A
	Former smoker	100	1.13 (1.09-1.16)	N/A	N/A
	Current Smoker	100	0.86 (0.82-0.91)	N/A	N/A
Body mass index category	<18.5	100	1.01 (0.86-1.18)	N/A	N/A
	18.5-24.9	100	Reference	N/A	N/A
	25-29.9	100	0.96 (0.92-1.00)	N/A	N/A
	30-39.9	100	0.85 (0.82-0.89)	N/A	N/A
	≥40	100	0.82 (0.76-0.88)	N/A	N/A
	Unknown	100	0.76 (0.70-0.82)	N/A	N/A
Systolic blood pressure category	<120	100	Reference	N/A	N/A

Predictor Variable	Predictor Class	KPNC Cohort		Ontario Cohort	
		Repetition %	Odds Ratio (95% CI)	Repetition %	Odds Ratio (95% CI)
	120-129	100	1.08 (1.02-1.13)	N/A	N/A
	130-139	100	1.14 (1.09-1.20)	N/A	N/A
	140-159	100	1.39 (1.33-1.46)	N/A	N/A
	160-180	100	1.47 (1.37-1.56)	N/A	N/A
	≥180	100	1.48 (1.31-1.68)	N/A	N/A
	Unknown	100	0.85 (0.78-0.93)	N/A	N/A
Prescription class	ACE inhibitor	100	Reference	100	Reference
	ACE inhibitor/ thiazide combination	100	1.20 (1.17-1.23)	100	0.81 (0.77-0.85)
	ARB	100	0.87 (0.84-0.91)	100	0.86 (0.84-0.88)
	ARB/ thiazide combination	100	1.05 (0.93-1.20)	100	0.76 (0.73-0.79)
Percentage of maximum daily dose		100	0.99 (0.99-0.99)	100	1.00 (0.99-1.00)
Beta blocker		100	1.14 (1.11-1.17)	<80	N/A
Calcium channel blocker prescription		100	1.20 (1.16-1.24)	100	1.09 (1.06-1.11)
Loop diuretic prescription		100	1.26 (1.19-1.33)	100	1.42 (1.37-1.47)
Thiazide diuretic		100	1.24 (1.21-1.28)	100	1.12 (1.09-1.15)
Potassium-sparing diuretic		<80	N/A	100	1.24 (1.19-1.30)
Alpha blocker		98	1.12 (1.07-1.18)	<80	N/A
Nitrates		<80	N/A	85	1.07 (1.03-1.12)
Anti-arrhythmic prescription		<80	N/A	97	1.17 (1.08-1.28)
Statin prescription		100	1.14 (1.11-1.17)	98	1.05 (1.03-1.07)
Other lipid-lowering agent		90	1.11 (1.04-1.17)	<80	N/A
NSAID		<80	N/A	100	0.90 (0.87-0.93)
Diabetic therapy		100	0.84 (0.81-0.87)	<80	N/A
eGFR category, mL/min/1.73 m^2	60-150	100	Reference	100	References
	45-59	100	1.11 (1.07-1.15)	100	1.06 (1.03-1.10)
	30-44	100	1.20 (1.13-1.27)	100	1.18 (1.11-1.25)
	15-29	100	1.42 (1.26-1.61)	100	1.21 (1.08-1.35)
	<15	100	1.79 (1.01-3.18)	100	1.06 (0.78-1.44)
Time from baseline serum creatinine to prescription date, days		<80	N/A	100	1.00 (1.00-1.00)
Baseline serum		100	0.90 (0.87-0.92)	100	0.92 (0.90-0.94)

Predictor Variable	Predictor Class	KPNC Cohort		Ontario Cohort	
		Repetition %	Odds Ratio (95% CI)	Repetition %	Odds Ratio (95% CI)
potassium value, mEq/L					
Hemoglobin	Unknown (no test)	100	1.04 (1.02-1.07)	100	1.17 (1.13-1.21)
	≥14	100	Reference	100	Reference
	13.0-13.9	100	0.97 (0.94-1.00)	100	1.03 (1.00-1.05)
	12.0-12.9	100	0.97 (0.93-1.01)	100	1.06 (1.03-1.09)
	11.0-11.9	100	0.99 (0.93-1.05)	100	1.11 (1.07-1.15)
	10.0-10.9	100	1.04 (0.94-1.15)	100	1.20 (1.13-1.26)
	9.0-9.9	100	1.13 (0.97-1.32)	100	1.33 (1.22-1.45)
	<9.0	100	1.60 (1.28-1.99)	100	1.29 (1.13-1.48)
Hemoglobin A1C category, %	Unknown (no test)	<80	N/A	100	0.99 (0.96-1.03)
	<6	<80	N/A	100	0.92 (0.89-0.95)
	6-<6.5	<80	N/A	100	0.96 (0.93-0.99)
	≥6.5	<80	N/A	100	Reference
Albumin-to-creatinine ratio, mg/mmol	Unknown (no test)	N/A	N/A	100	0.91 (0.89-0.94)
	Undetectable	N/A	N/A	100	0.96 (0.92-1.00)
	< 30	N/A	N/A	100	
	30-300	N/A	N/A	100	1.07 (1.03-1.11)
	>300	N/A	N/A	100	1.24 (1.16-1.33)
Number of previous visits to a family physician		100	1.02 (1.01-1.02)	100	1.00 (1.00-1.01)
Number of previous hospitalizations		100	1.15 (1.12-1.18)	<80	N/A
Number of previous emergency department visits		100	0.96 (0.95-0.98)	<80	N/A
Number of previous nephrology visits		100	1.12 (1.08-1.16)	100	1.04 (1.03-1.06)
Prescribing physician age		N/A	N/A	100	0.99 (0.98-0.99)
Prescribing physician gender	Unknown	N/A	N/A	100	1.01 (0.96-1.07)
	Men	N/A	N/A	100	Reference
	Women	N/A	N/A	100	1.12 (1.10-1.15)
Prescribing physician specialty	Nephrologist	N/A	N/A	100	1.70 (1.57-1.84)
	Primary care	N/A	N/A	100	Reference
	Cardiologist	N/A	N/A	100	1.33 (1.27-1.40)

Predictor Variable	Predictor Class	KPNC Cohort		Ontario Cohort	
		Repetition %	Odds Ratio (95% CI)	Repetition %	Odds Ratio (95% CI)
	Other/ Unknown	N/A	N/A	100	1.11 (1.06-1.16)
Prescribing physician a Canadian medical school graduate		N/A	N/A	100	1.13 (1.10-1.16)
Prescribing physician primary care provider type	Family Health Organization	N/A	N/A	97	0.93 (0.88-0.98)
	Family Health Group	N/A	N/A	97	Reference
	Family Health Network	N/A	N/A	97	1.00 (0.95-1.06)
	Comprehensive Care Model	N/A	N/A	97	1.04 (1.02-1.07)
	Other/ Unknown	N/A	N/A	97	1.00 (0.97-1.03)

Abbreviations: ACE, angiotensin converting enzyme; ADG, Aggregated Diagnostic Group; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; KPNC, Kaiser Permanente Northern California; NSAID, non-steroidal anti-inflammatory drug.

Appendix Table 9. All baseline characteristics for Kaiser Permanente Northern California cohort before and after matching, January 1, 2007 – December 31, 2015

Variable	Before matching			After matching		
	Follow-up tests (N=55,487)	No follow-up tests (N=108,767)	Stan. Diff.	Follow-up tests (N=54,274)	No follow-up tests (N=54,274)	Stan. Diff.
Demographic characteristics						
Age, year						
Mean (SD)	63.2 (13.7)	59.5 (13.9)	**27%**	63.0 (13.6)	63.0 (13.6)	<1%
Median (IQR)	63.5 (53.6-73.3)	59.1 (49.7-69.2)		63.3 (53.5-73.0)	63.3 (53.5-73.0)	
Age, No. (%), year						
18-<40	3139 (5.7)	9805 (9.0)	**13%**	3054 (5.6)	3058 (5.6)	<1%
40-<66	28,344 (51.1)	64,145 (59.0)	**16%**	28,076 (51.7)	28,074 (51.7)	<1%
66-<75	12,232 (22.0)	18,754 (17.2)	**12%**	11,982 (22.1)	11,978 (22.1)	<1%
75-<85	8885 (16.0)	12,308 (11.3)	**14%**	8522 (15.7)	8523 (15.7)	<1%
85+	2887 (5.2)	3755 (3.5)	8%	2640 (4.9)	2641 (4.9)	<1%
Gender, No. (%)						
Women	29,493 (53.2)	53,768 (49.4)	8%	28,842 (53.1)	28,653 (52.8)	1%
Men	25,994 (46.8)	54,999 (50.6)	8%	25,432 (46.9)	25,621 (47.2)	1%
Self-reported Race, No. (%)						
White	31,253 (56.3)	54,674 (50.3)	**12%**	30,427 (56.1)	30,083 (55.4)	1%
Black/African American	4174 (7.5)	11,111 (10.2)	**10%**	4102 (7.6)	4218 (7.8)	1%
Asian/Pacific Islander	9436 (17.0)	18,148 (16.7)	1%	9284 (17.1)	9091 (16.8)	1%
Other/Unknown	10,624 (19.1)	24,834 (22.8)	9%	10,461 (19.3)	10,882 (20.1)	2%
Hispanic ethnicity, No. (%)	7646 (13.8)	18,337 (16.9)	9%	7533 (13.9)	7838 (14.4)	1%
Household income <$35,000/year, No. (%)	3043 (5.5)	7189 (6.6)	5%	2965 (5.5)	3405 (6.3)	3%
Time from prescription date to index date, days						
Mean (SD)	11.7 (7.0)	11.6 (7.1)	1%	11.8 (7.0)	11.5 (7.1)	4%
Median (IQR)	10 (7-15)	10 (7-15)		10.0 (7.0-16.0)	10.0 (7.0-15.0)	
Year of prescription date, No. (%)						
2007	14,097 (25.4)	35,539 (32.7)	**16%**	13,887 (25.6)	17,154 (31.6)	**13%**
2008	7973 (14.4)	13,798 (12.7)	5%	7819 (14.4)	6728 (12.4)	6%
2009	6330 (11.4)	10,099 (9.3)	7%	6172 (11.4)	5046 (9.3)	7%
2010	5130 (9.3)	9112 (8.4)	3%	5001 (9.2)	4759 (8.8)	1%
2011	5230 (9.4)	8165 (7.5)	7%	5085 (9.4)	4335 (8.0)	5%
2012	4680 (8.4)	8083 (7.4)	4%	4550 (8.4)	4197 (7.7)	3%
2013	5175 (9.3)	9191 (8.5)	3%	5077 (9.4)	4758 (8.8)	2%
2014	3745 (6.8)	7747 (7.1)	1%	3636 (6.7)	3902 (7.2)	2%
2015	3127 (5.6)	7033 (6.5)	4%	3047 (5.6)	3395 (6.3)	3%
Medical history in the 5 years prior to or on prescription date (unless otherwise specified), No. (%)						
Acute myocardial infarction	1357 (2.4)	1668 (1.5)	7%	1214 (2.2)	1028 (1.9)	2%

Heart failure	3007 (5.4)	2830 (2.6)	**14%**	2535 (4.7)	2038 (3.8)	4%
Ischemic stroke or transient ischemic attack	1002 (1.8)	1612 (1.5)	2%	943 (1.7)	1009 (1.9)	2%
Peripheral arterial disease	341 (0.6)	463 (0.4)	3%	315 (0.6)	299 (0.6)	<1%
Mitral and/or aortic valvular disease	2004 (3.6)	2061 (1.9)	**10%**	1772 (3.3)	1416 (2.6)	4%
Atrial flutter or fibrillation	3442 (6.2)	3117 (2.9)	**16%**	2938 (5.4)	2341 (4.3)	5%
Ventricular tachycardia or fibrillation	43 (0.1)	74 (0.1)	<1%	39 (0.1)	49 (0.1)	<1%
Coronary artery bypass graft surgery	622 (1.1)	780 (0.7)	4%	559 (1.0)	466 (0.9)	1%
Percutaneous coronary intervention	1570 (2.8)	2018 (1.9)	6%	1467 (2.7)	1245 (2.3)	3%
Diabetes mellitus	11,010 (19.8)	22,185 (20.4)	1%	10,844 (20.0)	10,347 (19.1)	2%
Hypertension	44,078 (79.4)	80,556 (74.1)	**13%**	43,148 (79.5)	41,927 (77.3)	5%
Dyslipidemia	33,610 (60.6)	61,605 (56.6)	8%	32,779 (60.4)	32,296 (59.5)	2%
Hyperthyroidism	441 (0.8)	775 (0.7)	1%	421 (0.8)	425 (0.8)	<1%
Hypothyroidism	6958 (12.5)	10,969 (10.1)	8%	6712 (12.4)	6499 (12.0)	1%
Cancer	2746 (4.9)	3564 (3.3)	8%	2646 (4.9)	2195 (4.0)	4%
Cirrhosis	283 (0.5)	382 (0.4)	1%	272 (0.5)	207 (0.4)	1%
Chronic lung disease	9654 (17.4)	17,383 (16.0)	4%	9282 (17.1)	9358 (17.2)	<1%
Dementia	785 (1.4)	1428 (1.3)	1%	749 (1.4)	898 (1.7)	2%
Depression	6290 (11.3)	12,483 (11.5)	1%	6131 (11.3)	6445 (11.9)	2%
Hospitalized bleed	984 (1.8)	1421 (1.3)	4%	924 (1.7)	868 (1.6)	1%
Smoking status						
Current Smoker	2413 (4.3)	4821 (4.4)	<1%	2362 (4.4)	2186 (4.0)	2%
Former smoker	10,977 (19.8)	13,945 (12.8)	**19%**	10,619 (19.6)	8079 (14.9)	**12%**
Non-smoker	42,097 (75.9)	90,001 (82.7)	**17%**	41,293 (76.1)	44,009 (81.1)	**12%**
Health status measures in the one year prior						
Body mass index, No. (%), kg/m^2						
<18.5	328 (0.6)	353 (0.3)	4%	310 (0.6)	224 (0.4)	3%
18.5-<25	7811 (14.1)	9691 (8.9)	**16%**	7589 (14.0)	5727 (10.6)	10%
25-<30	12,367 (22.3)	17,119 (15.7)	**17%**	12,085 (22.3)	9401 (17.3)	**13%**
30-<40	11,725 (21.1)	19,994 (18.4)	7%	11,509 (21.2)	10,101 (18.6)	7%
≥40	1521 (2.7)	2908 (2.7)	<1%	1491 (2.7)	1288 (2.4)	2%
Unknown	21,735 (39.2)	58,702 (54.0)	**30%**	21,290 (39.2)	27,533 (50.7)	**23%**
Systolic blood pressure, No. (%), mmHg						
<120	4692 (8.5)	8079 (7.4)	4%	4412 (8.1)	4217 (7.8)	1%
120-<130	4830 (8.7)	8396 (7.7)	4%	4712 (8.7)	4365 (8.0)	3%
130-<140	8662 (15.6)	13,959 (12.8)	8%	8489 (15.6)	7443 (13.7)	5%
140-<160	12,761 (23.0)	16,549 (15.2)	**20%**	12,584 (23.2)	8926 (16.4)	**17%**
160-<180	2998 (5.4)	3758 (3.5)	9%	2959 (5.5)	2086 (3.8)	8%
≥180	534 (1.0)	674 (0.6)	4%	532 (1.0)	386 (0.7)	3%
Unknown	21,010 (37.9)	57,352 (52.7)	**30%**	20,586 (37.9)	26,851 (49.5)	**24%**
Prescription characteristics						
Prescription class, No. (%)						

ACE inhibitor	33,471 (60.3)	64,772 (59.6)	1%	32,447 (59.8)	32,964 (60.7)	2%
ACE inhibitor / thiazide combination	15,843 (28.6)	30,042 (27.6)	2%	15,776 (29.1)	14,750 (27.2)	4%
ARB	6169 (11.1)	13,908 (12.8)	5%	5680 (10.5)	6128 (11.3)	3%
ARB / thiazide combination	4 (0.0)	45 (0.0)	<1%	371 (0.7)	432 (0.8)	1%
Percentage of maximum daily dose						
Mean (SD)	26.5 (17.8)	31.5 (23.2)	**23%**	26.6 (17.8)	31.2 (23.2)	**22%**
Median (IQR)	25.0 (12.5-25.0)	25.0 (12.5-50.0)		25.0 (12.5-25.0)	25.0 (12.5-50.0)	
Baseline medication use in the 120 days prior to or on prescription date, n (%)						
Beta blocker	18,239 (32.9)	27,405 (25.2)	**17%**	17,503 (32.2)	16,553 (30.5)	4%
Calcium channel blocker	7704 (13.9)	11,682 (10.7)	**10%**	7339 (13.5)	6989 (12.9)	2%
Loop diuretic	3868 (7.0)	4360 (4.0)	**13%**	3385 (6.2)	3096 (5.7)	2%
Thiazide diuretic	19,622 (35.4)	31,017 (28.5)	**15%**	19,150 (35.3)	18,203 (33.5)	4%
Potassium-sparing diuretic	399 (0.7)	551 (0.5)	3%	362 (0.7)	368 (0.7)	<1%
Alpha blocker	3443 (6.2)	5087 (4.7)	7%	3273 (6.0)	3268 (6.0)	<1%
Any anti-hypertensive agent	35,413 (63.8)	57,931 (53.3)	**21%**	34,342 (63.3)	33,194 (61.2)	4%
Nitrates	1123 (2.0)	1504 (1.4)	5%	1019 (1.9)	993 (1.8)	1%
Antiarrhythmic drug	515 (0.9)	427 (0.4)	6%	442 (0.8)	340 (0.6)	2%
Statin	22,833 (41.2)	38,457 (35.4)	**12%**	22,175 (40.9)	21,619 (39.8)	2%
Other lipid-lowering agent	2019 (3.6)	3462 (3.2)	2%	1966 (3.6)	1804 (3.3)	2%
Non-aspirin antiplatelet agent	1390 (2.5)	1990 (1.8)	5%	1313 (2.4)	1253 (2.3)	1%
Low molecular weight heparin	287 (0.5)	253 (0.2)	5%	247 (0.5)	171 (0.3)	3%
NSAID	8126 (14.6)	15,804 (14.5)	<1%	7992 (14.7)	7782 (14.3)	1%
Diabetic therapy	5771 (10.4)	14,871 (13.7)	**10%**	5661 (10.4)	6062 (11.2)	3%
Baseline laboratory values in the one year prior to or on prescription date						
eGFR, mL/min/1.73 m^2						
Mean (SD)	78.4 (20.5)	83.1 (20.2)	**23%**	78.9 (20.1)	78.9 (20.1)	<1%
Median (IQR)	80.0 (64.7-93.2)	84.6 (69.7-97.8)		80.4 (65.2-93.4)	80.4 (65.3-93.4)	
eGFR, No. (%), mL/min/1.73 m^2						
60-150	44,914 (81.0)	94,022 (86.4)	**15%**	44,370 (81.8)	44,387 (81.8)	<1%
45-<60	7085 (12.8)	10,454 (9.6)	**10%**	6816 (12.6)	6808 (12.5)	<1%
30-<45	2799 (5.0)	3585 (3.3)	9%	2577 (4.7)	2568 (4.7)	<1%
15-<30	660 (1.2)	680 (0.6)	6%	499 (0.9)	502 (0.9)	<1%
<15	29 (0.1)	26 (0.0)	4%	12 (0.0)	9 (0.0)	<1%
Serum creatinine, mg/dL						
Mean (SD)	1.0 (0.3)	0.9 (0.3)	**10%**	0.9 (0.3)	0.9 (0.3)	<1%
Median (IQR)	0.9 (0.8-1.1)	0.9 (0.8-1.0)		0.9 (0.8-1.1)	0.9 (0.8-1.1)	
Time from baseline serum creatinine to prescription date, days						
Mean (SD)	107.4 (108.5)	84.7 (99.8)	**22%**	108 (109)	86 (99)	**21%**
Median (IQR)	67.0 (13.0-185.0)	37.0 (5.0-143.0)		69 (13-186)	41 (6-144)	

Serum potassium, mEq/L						
Mean (SD)	4.3 (0.4)	4.3 (0.4)	8%	4.3 (0.4)	4.3 (0.4)	3%
Median (IQR)	4.3 (4.0-4.6)	4.3 (4.1-4.6)		4.3 (4.0-4.6)	4.3 (4.1-4.5)	
Serum potassium, No. (%), mEq/L						
<5.0	52,474 (94.6)	102,487 (94.2)	2%	51,433 (94.8)	51,433 (94.8)	<1%
5.0-5.5	3013 (5.4)	6280 (5.8)	2%	2841 (5.2)	2841 (5.2)	<1%
Time from baseline potassium to prescription date, days						
Mean (SD)	114.4 (111.1)	92.4 (104.5)	**21%**	116 (112)	94 (103)	**21%**
Median (IQR)	77.0 (14.3-199.1)	42.9 (5.5-159.5)		79 (14-201)	50 (7-161)	
Hemoglobin category, No. (%), g/L						
≥14	22,358 (40.3)	45,498 (41.8)	3%	22,010 (40.6)	21,901 (40.4)	<1%
13.0-<14	9960 (18.0)	18,445 (17.0)	3%	9752 (18.0)	9788 (18.0)	<1%
12.0-<13	5522 (10.0)	9765 (9.0)	3%	5346 (9.9)	5391 (9.9)	<1%
11.0-<12	2263 (4.1)	3735 (3.4)	4%	2129 (3.9)	2065 (3.8)	1%
10.0-<11	821 (1.5)	1231 (1.1)	4%	751 (1.4)	666 (1.2)	2%
9.0-<10	314 (0.6)	437 (0.4)	3%	285 (0.5)	232 (0.4)	1%
<9.0	175 (0.3)	194 (0.2)	2%	155 (0.3)	90 (0.2)	2%
Unknown	14,074 (25.4)	29,462 (27.1)	4%	13,846 (25.5)	14,141 (26.1)	1%
Baseline healthcare utilization in the one year on and prior to prescription date						
Primary care visits						
Mean (SD)	4.8 (5.4)	4.1 (4.3)	**16%**	4.7 (5.3)	4.3 (4.5)	8%
Median (IQR)	3.0 (2.0-6.0)	3.0 (1.0-5.0)		3.0 (2.0-6.0)	3.0 (2.0-6.0)	
Range	0.0-103.0	0.0-101.0		0.0-103.0	0.0-101.0	
Hospitalizations						
Mean (SD)	0.2 (0.6)	0.1 (0.5)	**14%**	0.2 (0.6)	0.2 (0.6)	5%
Median (IQR)	0.0 (0.0-0.0)	0.0 (0.0-0.0)		0.0 (0.0-0.0)	0.0 (0.0-0.0)	
Range	0.0-14.0	0.0-16.0		0.0-14.0	0.0-16.0	
Emergency department visits						
Mean (SD)	0.4 (1.0)	0.3 (0.9)	8%	0.4 (0.9)	0.4 (0.9)	3%
Median (IQR)	0.0 (0.0-1.0)	0.0 (0.0-0.0)		0.0 (0.0-0.0)	0.0 (0.0-0.0)	
Range	0.0-38.0	0.0-34.0		0.0-38.0	0.0-34.0	
Nephrology visits						
Mean (SD)	0.0 (0.4)	0.0 (0.3)	7%	0.0 (0.4)	0.0 (0.3)	4%
Median (IQR)	0.0 (0.0-0.0)	0.0 (0.0-0.0)		0.0 (0.0-0.0)	0.0 (0.0-0.0)	
Range	0.0-19.0	0.0-12.0		0.0-19.0	0.0-8.0	

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; KPNC, Kaiser Permanente Northern California; IQR, interquartile range; NSAID, non-steroidal anti-inflammatory drug; SD, standard deviation; Stan. Diff., standardized difference.

Appendix Table 10. All baseline characteristics for Ontario cohort before and after matching, January 1, 2007 – December 31, 2015

Variable	Before matching			After matching		
	Follow-up tests (N=60,277)	No follow-up tests (N=217,906)	Stan. Diff.	Follow-up tests (N=59,520)	No follow-up tests (N=59,520)	Stan. Diff.
Demographic characteristics						
Age, year						
Mean (SD)	75.5 (7.0)	74.6 (6.9)	**14%**	75.5 (6.9)	75.4 (6.9)	<1%
Median (IQR)	74 (70-80)	73 (69-79)		74 (70-80)	74 (70-80)	
Age, No. (%), year						
66-<75	30,325 (50.3)	121,471 (55.7)	**11%**	30,079 (50.5)	30,087 (50.5)	<1%
75-<85	22,552 (37.4)	74,456 (34.2)	7%	22,318 (37.5)	22,328 (37.5)	<1%
85+	7400 (12.3)	21,979 (10.1)	7%	7123 (12.0)	7105 (11.9)	<1%
Gender, No. (%)						
Women	31,538 (52.3)	114,721 (52.6)	1%	31,166 (52.4)	31,593 (53.1)	1%
Men	28,739 (47.7)	103,185 (47.4)	1%	28,354 (47.6)	27,927 (46.9)	1%
Income quintile, No. (%)*						
1 (lowest)	11,124 (18.5)	40,200 (18.4)	<1%	10,988 (18.5)	11,024 (18.5)	<1%
2	12,518 (20.8)	44,676 (20.5)	1%	12,347 (20.7)	12,358 (20.8)	<1%
3	12,083 (20.0)	44,053 (20.2)	<1%	11,955 (20.1)	11,882 (20.0)	<1%
4	12,409 (20.6)	44,869 (20.6)	<1%	12,255 (20.6)	12,230 (20.5)	<1%
5 (highest)	12,143 (20.1)	44,108 (20.2)	<1%	11,975 (20.1)	12,026 (20.2)	<1%
Rural residence, No. (%)†	8528 (14.1)	27,042 (12.4)	5%	8409 (14.1)	8303 (13.9)	1%
Local Health Integration Network, No. (%)						
1	1529 (2.5)	7996 (3.7)	7%	1510 (2.5)	1478 (2.5)	<1%
2	5660 (9.4)	17,344 (8.0)	5%	5552 (9.3)	5436 (9.1)	1%
3	3579 (5.9)	10,085 (4.6)	6%	3513 (5.9)	3487 (5.9)	<1%
4	6407 (10.6)	24,889 (11.4)	3%	6367 (10.7)	6462 (10.9)	1%
5	3591 (6.0)	13,418 (6.2)	1%	3558 (6.0)	3718 (6.2)	1%
6	4778 (7.9)	17,985 (8.3)	1%	4708 (7.9)	4701 (7.9)	<1%
7	4293 (7.1)	17,540 (8.0)	3%	4243 (7.1)	4295 (7.2)	<1%
8	7862 (13.0)	30,425 (14.0)	3%	7761 (13.0)	7726 (13.0)	<1%
9	8335 (13.8)	29,799 (13.7)	<1%	8207 (13.8)	8258 (13.9)	<1%
10	3268 (5.4)	9939 (4.6)	4%	3229 (5.4)	3106 (5.2)	1%
11	5134 (8.5)	18,695 (8.6)	<1%	5096 (8.6)	5110 (8.6)	<1%
12	2584 (4.3)	8317 (3.8)	3%	2557 (4.3)	2544 (4.3)	<1%
13	2459 (4.1)	8755 (4.0)	1%	2430 (4.1)	2439 (4.1)	<1%
14	798 (1.3)	2719 (1.2)	1%	789 (1.3)	760 (1.3)	<1%
Time from prescription date to index date, days						
Mean (SD)	11.3 (8.3)	12.6 (8.5)	**15%**	11.3 (8.3)	12.4 (8.5)	**13%**
Median (IQR)	9 (4-17)	11 (5-20)		10 (4-17)	11 (5-19)	
Year of prescription date, No. (%)						
2007	53 (0.1)	361 (0.2)	3%	52 (0.1)	87 (0.1)	<1%
2008	1850 (3.1)	9614 (4.4)	7%	1836 (3.1)	2268 (3.8)	4%
2009	5462 (9.1)	21,849 (10.0)	3%	5423 (9.1)	5202 (8.7)	1%
2010	7821 (13.0)	29,034 (13.3)	1%	7763 (13.0)	7471 (12.6)	1%
2011	8199 (13.6)	28,463 (13.1)	1%	8129 (13.7)	7529 (12.6)	3%

2012	9261 (15.4)	33,813 (15.5)	<1%	9159 (15.4)	9953 (16.7)	4%
2013	9520 (15.8)	31,280 (14.4)	4%	9395 (15.8)	8889 (14.9)	2%
2014	10,316 (17.1)	32,124 (14.7)	7%	10,116 (17.0)	9198 (15.5)	4%
2015	7795 (12.9)	31,368 (14.4)	4%	7647 (12.8)	8923 (15.0)	6%
Residing in OLIS catchment area, No. (%)	9212 (15.3)	32,597 (15.0)	1%	8910 (15.0)	8910 (15.0)	<1%
Medical history in the 5 years prior to or on prescription date (unless otherwise specified), No. (%)						
Johns Hopkins ADG score in the 2 years prior to or on prescription date						
Mean (SD)	7.9 (3.8)	7.3 (3.7)	**14%**	7.8 (3.8)	7.8 (3.8)	1%
Median (IQR)	8 (5-10)	7 (5-10)		8 (5-10)	7 (5-10)	
Charlson comorbidity score						
0 or no hospitalization	41,194 (68.3)	161,633 (74.2)	**13%**	40,942 (68.8)	41,092 (69.0)	<1%
1	7482 (12.4)	24,751 (11.4)	3%	7376 (12.4)	7507 (12.6)	1%
2	5742 (9.5)	17,165 (7.9)	6%	5615 (9.4)	5587 (9.4)	<1%
3 or more	5859 (9.7)	14,357 (6.6)	**11%**	5587 (9.4)	5334 (9.0)	1%
Acute myocardial infarction	1984 (3.3)	6093 (2.8)	3%	1911 (3.2)	1974 (3.3)	1%
Heart failure	8212 (13.6)	20,285 (9.3)	**14%**	7833 (13.2)	7686 (12.9)	1%
Ischemic stroke or transient ischemic attack	2524 (4.2)	7642 (3.5)	4%	2454 (4.1)	2499 (4.2)	1%
Peripheral arterial disease	970 (1.6)	2739 (1.3)	3%	943 (1.6)	957 (1.6)	<1%
Mitral and/or aortic valvular disease	1299 (2.2)	3026 (1.4)	6%	1239 (2.1)	1185 (2.0)	1%
Atrial flutter or fibrillation	4458 (7.4)	10,609 (4.9)	**10%**	4252 (7.1)	4084 (6.9)	1%
Ventricular tachycardia or fibrillation	267 (0.4)	699 (0.3)	2%	258 (0.4)	253 (0.4)	<1%
Coronary artery bypass graft surgery	1426 (2.4)	3981 (1.8)	4%	1386 (2.3)	1333 (2.2)	1%
Percutaneous coronary intervention	1861 (3.1)	6203 (2.8)	2%	1829 (3.1)	1880 (3.2)	1%
Diabetes mellitus	25,307 (42.0)	84,776 (38.9)	6%	24,893 (41.8)	25,083 (42.1)	1%
Hypertension	50,713 (84.1)	183,889 (84.4)	1%	50,053 (84.1)	50,318 (84.5)	1%
Dyslipidemia	19,468 (32.3)	70,561 (32.4)	<1%	19,296 (32.4)	19,199 (32.3)	<1%
Hyperthyroidism	1154 (1.9)	3894 (1.8)	1%	1139 (1.9)	1102 (1.9)	<1%
Hypothyroidism	5638 (9.4)	18,341 (8.4)	4%	5538 (9.3)	5306 (8.9)	1%
Cancer	8704 (14.4)	26,463 (12.1)	7%	8567 (14.4)	7966 (13.4)	3%
Cirrhosis	585 (1.0)	1480 (0.7)	3%	575 (1.0)	467 (0.8)	2%
Chronic lung disease	13,506 (22.4)	44,313 (20.3)	5%	13,236 (22.2)	13,206 (22.2)	<1%
Dementia	5732 (9.5)	16,519 (7.6)	7%	5514 (9.3)	5371 (9.0)	1%
Depression	888 (1.5)	2639 (1.2)	3%	849 (1.4)	848 (1.4)	<1%
Hospitalized bleed	6969 (11.6)	21,907 (10.1)	5%	6815 (11.4)	6781 (11.4)	<1%
Prescription characteristics						
Prescription class, No. (%)						
ACE inhibitor	36,061 (59.8)	119,271 (54.7)	**10%**	35,573 (59.8)	33,089 (55.6)	9%

ACE inhibitor / thiazide combination	3091 (5.1)	13,378 (6.1)	4%	3074 (5.2)	3339 (5.6)	2%
ARB	16,870 (28.0)	65,286 (30.0)	4%	16,642 (28.0)	18,025 (30.3)	5%
ARB / thiazide combination	4255 (7.1)	19,971 (9.2)	8%	4231 (7.1)	5067 (8.5)	5%
Percentage of maximum daily dose						
Mean (SD)	51.4 (28.6)	55.7 (29.5)	**15%**	51.5 (28.6)	55.5 (29.8)	**14%**
Median (IQR)	50 (25-50)	50 (25-100)		50 (25-50)	50 (25-100)	
Baseline medication use in the 120 days prior to or on prescription date, n (%)						
Beta blocker	18,555 (30.8)	58,686 (26.9)	9%	18,163 (30.5)	17,839 (30.0)	1%
Calcium channel blocker	18,233 (30.2)	59,831 (27.5)	6%	17,865 (30.0)	17,988 (30.2)	<1%
Loop diuretic	7659 (12.7)	15,889 (7.3)	**18%**	7269 (12.2)	6153 (10.3)	6%
Thiazide diuretic	18,711 (31.0)	70,687 (32.4)	3%	18,538 (31.1)	18,809 (31.6)	1%
Potassium-sparing diuretic	3143 (5.2)	8113 (3.7)	7%	3053 (5.1)	2464 (4.1)	5%
Alpha blocker	1805 (3.0)	5484 (2.5)	3%	1737 (2.9)	1721 (2.9)	<1%
Any anti-hypertensive agent	41,316 (68.5)	140,790 (64.6)	8%	40,638 (68.3)	40,250 (67.6)	2%
Nitrates	3579 (5.9)	9646 (4.4)	7%	3475 (5.8)	3000 (5.0)	4%
Antiarrhythmic drug	916 (1.5)	1978 (0.9)	6%	875 (1.5)	745 (1.3)	2%
Statin	33,160 (55.0)	114,486 (52.5)	5%	32,706 (54.9)	32,903 (55.3)	1%
Other lipid-lowering agent	4102 (6.8)	13,856 (6.4)	2%	4055 (6.8)	4069 (6.8)	<1%
Non-aspirin antiplatelet agent	3904 (6.5)	11,885 (5.5)	4%	3835 (6.4)	3672 (6.2)	1%
Low molecular weight heparin	224 (0.4)	521 (0.2)	4%	215 (0.4)	173 (0.3)	2%
NSAID	6310 (10.5)	25,887 (11.9)	4%	6268 (10.5)	6909 (11.6)	4%
Diabetic therapy	15,567 (25.8)	51,964 (23.8)	5%	15,299 (25.7)	15,712 (26.4)	2%
Baseline laboratory values in the one year prior to or on prescription date						
eGFR, mL/min/1.73 m^2						
Mean (SD)	68.3 (18.7)	71.3 (17.1)	**17%**	68.6 (18.5)	68.6 (18.4)	<1%
Median (IQR)	71.0 (55.0-84.0)	74.0 (60.0-85.0)		71.0 (56.0-84.0)	71.0 (56.0-84.0)	
eGFR, No. (%), mL/min/1.73 m^2						
60-150	41,166 (68.3)	163,222 (74.9)	**11%**	40,955 (68.8)	40,955 (68.8)	<1%
45-<60	11,182 (18.6)	36,478 (16.7)	5%	11,059 (18.6)	11,059 (18.6)	<1%
30-<45	5932 (9.8)	14,714 (6.8)	**11%**	5750 (9.7)	5782 (9.7)	<1%
15-<30	1849 (3.1)	3303 (1.5)	**11%**	1675 (2.8)	1653 (2.8)	<1%
<15	148 (0.2)	189 (0.1)	3%	81 (0.1)	71 (0.1)	<1%
Serum creatinine, mg/dL						
Mean (SD)	1.0 (0.4)	0.9 (0.3)	**16%**	1.0 (0.4)	1.0 (0.4)	1%
Median (IQR)	0.9 (0.8-1.1)	0.9 (0.8-1.1)		0.9 (0.8-1.1)	0.9 (0.7-1.1)	
Time from baseline serum creatinine to prescription date, days						
Mean (SD)	133 (113)	109 (103)	**23%**	134 (113)	106 (102)	**26%**
Median (IQR)	103 (28-222)	72 (20-186)	**22%**	104 (28-223)	69 (19-181)	
Serum potassium, mEq/L						
Mean (SD)	4.4 (0.4)	4.4 (0.4)	2%	4.4 (0.4)	4.4 (0.4)	2%
Median (IQR)	4.0 (4.0-5.0)	4.0 (4.0-5.0)		4.0 (4.0-5.0)	4.0 (4.0-5.0)	

Serum potassium, No. (%), mEq/L						
<5.0	54,992 (91.2)	199,133 (91.4)	<1%	54,440 (91.5)	54,440 (91.5)	<1%
5.0-5.5	5285 (8.8)	18,773 (8.6)	<1%	5080 (8.5)	5080 (8.5)	<1%
Time from baseline potassium to prescription date, days						
Mean (SD)	139 (114)	117 (107)	**20%**	140 (115)	115 (106)	**23%**
Median (IQR)	112 (30-231)	83 (22-200)		114 (31-232)	80 (22-197)	
Hemoglobin A1C category, %						
Mean (SD)	6.5 (1.2)	6.5 (1.2)	4%	6.5 (1.2)	6.5 (1.2)	<1%
Median (IQR)	6.0 (6.0-7.0)	6.0 (6.0-7.0)		6.0 (6.0-7.0)	6.0 (6.0-7.0)	
Unknown, n (%)	22,096 (36.7)	77,815 (35.7)	2%	21,877 (36.8)	20,293 (34.1)	6%
Albumin-to-creatinine ratio, No. (%), mg/mmol						
Undetectable	4356 (7.2)	16,331 (7.5)	1%	4315 (7.2)	4529 (7.6)	2%
<30	9501 (15.8)	34,369 (15.8)	<1%	9921 (16.7)	9979 (16.8)	<1%
30-300	5672 (9.4)	17,322 (7.9)	5%	5197 (8.7)	5196 (8.7)	<1%
>300	1844 (3.1)	3999 (1.8)	8%	1609 (2.7)	1350 (2.3)	3%
Unknown	38,904 (64.5)	145,885 (66.9)	5%	38,478 (64.6)	38,466 (64.6)	<1%
Baseline healthcare utilization in the one year on and prior to prescription date						
Primary care visits						
Mean (SD)	8.9 (9.1)	8.0 (7.7)	**12%**	8.8 (9.0)	8.6 (8.4)	3%
Median (IQR)	7 (4-11)	6 (4-10)		7 (4-11)	7 (4-11)	
Range	0-200	0-204		0-200	0-177	
Hospitalizations						
Mean (SD)	0.2 (0.6)	0.2 (0.5)	**10%**	0.2 (0.6)	0.2 (0.6)	3%
Median (IQR)	0 (0-0)	0 (0-0)		0 (0-0)	0 (0-0)	
Range	0-9	0-10		0-9	0-10	
Emergency department visits						
Mean (SD)	0.7 (1.3)	0.5 (1.2)	**10%**	0.7 (1.3)	0.6 (1.3)	3%
Median (IQR)	0 (0-1)	0 (0-1)		0 (0-1)	0 (0-1)	
Range	0-31	0-49		0-31	0-33	
Nephrology visits						
Mean (SD)	0.3 (1.1)	0.1 (0.7)	**12%**	0.2 (1.0)	0.2 (0.9)	2%
Median (IQR)	0 (0-0)	0 (0-0)		0 (0-0)	0 (0-0)	
Range	0-45	0-51		0-45	0-35	
Prescribing physician characteristics						
Physician age, years						
Mean (SD)	53.2 (10.5)	55.1 (10.4)	**19%**	53.2 (10.5)	54.9 (10.4)	**17%**
Median (IQR)	53 (45-61)	56 (48-63)		53 (45-61)	55 (47-62)	
Unknown, n (%)	10,130 (16.8)	31,051 (14.2)	7%	9986 (16.8)	8698 (14.6)	6%
Physician gender, No. (%)						
Women	14,513 (24.1)	47,835 (22.0)	5%	14,364 (24.1)	13,170 (22.1)	5%
Men	35,634 (59.1)	139,020 (63.8)	**10%**	35,170 (59.1)	37,652 (63.3)	9%
Unknown	10,130 (16.8)	31,051 (14.2)	7%	9986 (16.8)	8698 (14.6)	6%
Physician rural practice location, No. (%)	4770 (7.9)	15,411 (7.1)	3%	4703 (7.9)	4578 (7.7)	1%
Unknown	10,130 (16.8)	31,041 (14.2)	7%	9986 (16.8)	8696 (14.6)	6%
Physician specialty, No. (%)						
Nephrologist	1448 (2.4)	2118 (1.0)	**11%**	1365 (2.3)	993 (1.7)	4%
Primary care	40,656 (67.4)	160,143 (73.5)	**13%**	40,250 (67.6)	42,624 (71.6)	9%
Cardiologist	3970 (6.6)	11,187 (5.1)	6%	3916 (6.6)	3300 (5.5)	5%
Other	4073 (6.8)	13,417 (6.2)	2%	4003 (6.7)	3907 (6.6)	<1%

Unknown	10,130 (16.8)	31,041 (14.2)	7%	9986 (16.8)	8696 (14.6)	6%
Canadian medical school graduate, No. (%)	37,569 (62.3)	132,713 (60.9)	3%	37,095 (62.3)	36,637 (61.6)	1%
Unknown	10,130 (16.8)	31,051 (14.2)	7%	9986 (16.8)	8698 (14.6)	6%
Time since graduation, years						
Mean (SD)	26.8 (10.9)	28.8 (10.8)	**18%**	26.9 (10.9)	28.6 (10.8)	**16%**
Median (IQR)	27 (19-35)	29 (21-37)		27 (19-35)	29 (21-36)	
Unknown, n (%)	10,130 (16.8)	31,055 (14.3)	7%	9986 (16.8)	8701 (14.6)	6%
Primary care provider type, No. (%)						
Family Health Organization	20,515 (34.0)	73,938 (33.9)	<1%	20,281 (34.1)	20,193 (33.9)	<1%
Family Health Group	17,359 (28.8)	71,335 (32.7)	8%	17,212 (28.9)	18,470 (31.0)	5%
Family Health Network	2051 (3.4)	7065 (3.2)	1%	2021 (3.4)	2149 (3.6)	1%
Comprehensive Care Model	1721 (2.9)	7568 (3.5)	3%	1701 (2.9)	2055 (3.5)	3%
Other	1342 (2.2)	4383 (2.0)	1%	1334 (2.2)	1177 (2.0)	1%
Unknown	17,289 (28.7)	53,617 (24.6)	9%	16,971 (28.5)	15,476 (26.0)	6%

Abbreviations: ACE, angiotensin converting enzyme; ADG, Aggregated Diagnostic Group; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; KPNC, Kaiser Permanente Northern California; IQR, interquartile range; NSAID, non-steroidal anti-inflammatory drug; OLIS, Ontario Laboratories Information System; SD, standard deviation; Stan. Diff., standardized difference.

* Missing imputed into the middle (third) income quintile.

† Missing categorized as not rural.

Appendix Table 11. Baseline characteristics for patients >66 years of age in the KPNC cohort

Variable	Overall (N=46,286)	Follow-up tests (N=23,144)	No follow-up tests (N=23,142)	Stan. Diff.
Demographic characteristics				
Age, year				
Mean (SD)	75.7 (6.8)	75.8 (6.8)	75.7 (6.8)	<1%
Median (IQR)	74.7 (70.0-80.6)	74.7 (70.0-80.6)	74.7 (70.0-80.6)	
Range	66.0-104.0	66.0-104.0	66.0-103.0	
Age, No. (%), year				
66-<76	23,960 (51.8)	11,982 (51.8)	11,978 (51.8)	<1%
76-<85	17,045 (36.8)	8522 (36.8)	8523 (36.8)	<1%
85+	5281 (11.4)	2640 (11.4)	2641 (11.4)	<1%
Gender, No. (%)				
Women	26,842 (58.0)	13,309 (57.5)	13,533 (58.5)	2%
Men	19,444 (42.0)	9835 (42.5)	9609 (41.5)	2%
Self-reported Race, No. (%)				
White	30,185 (65.2)	15,183 (65.6)	15,002 (64.8)	2%
Black/African American	2791 (6.0)	1404 (6.1)	1387 (6.0)	<1%
Asian/Pacific Islander	5753 (12.4)	2801 (12.1)	2952 (12.8)	2%
Other/Unknown	7557 (16.3)	3756 (16.2)	3801 (16.4)	1%
Hispanic ethnicity, No. (%)	5228 (11.3)	2626 (11.3)	2602 (11.2)	<1%
Household income below $35,000/year	2734 (5.9)	1254 (5.4)	1480 (6.4)	4%
Year of prescription date				
2007	14,237 (30.8)	6184 (26.7)	8053 (34.8)	**18%**
2008	5949 (12.9)	3248 (14.0)	2701 (11.7)	7%
2009	4498 (9.7)	2496 (10.8)	2002 (8.7)	7%
2010	3885 (8.4)	1959 (8.5)	1926 (8.3)	1%
2011	4124 (8.9)	2298 (9.9)	1826 (7.9)	7%
2012	3730 (8.1)	2010 (8.7)	1720 (7.4)	5%
2013	4446 (9.6)	2300 (9.9)	2146 (9.3)	2%
2014	3085 (6.7)	1500 (6.5)	1585 (6.8)	1%
2015	2332 (5.0)	1149 (5.0)	1183 (5.1)	<1%
Medical history in the 5 years prior to or on prescription date, No. (%)				
Acute myocardial infarction	1444 (3.1)	782 (3.4)	662 (2.9)	3%
Heart failure	3609 (7.8)	1980 (8.6)	1629 (7.0)	6%
Ischemic stroke or transient ischemic attack	1475 (3.2)	694 (3.0)	781 (3.4)	2%
Peripheral arterial disease	457 (1.0)	234 (1.0)	223 (1.0)	<1%
Mitral and/or aortic valvular disease	2363 (5.1)	1325 (5.7)	1038 (4.5)	5%
Atrial flutter or fibrillation	4268 (9.2)	2363 (10.2)	1905 (8.2)	7%
Ventricular tachycardia or fibrillation	52 (0.1)	27 (0.1)	25 (0.1)	<1%
Coronary artery bypass graft surgery	655 (1.4)	360 (1.6)	295 (1.3)	3%
Percutaneous coronary	1561 (3.4)	833 (3.6)	728 (3.1)	3%

intervention				
Diabetes mellitus	9538 (20.6)	4935 (21.3)	4603 (19.9)	3%
Hypertension	38,301 (82.7)	19,343 (83.6)	18,958 (81.9)	5%
Dyslipidemia	32,092 (69.3)	16,246 (70.2)	15,846 (68.5)	4%
Hyperthyroidism	343 (0.7)	165 (0.7)	178 (0.8)	1%
Hypothyroidism	7902 (17.1)	4084 (17.6)	3818 (16.5)	3%
Cancer	3089 (6.7)	1643 (7.1)	1446 (6.2)	4%
Cirrhosis	217 (0.5)	118 (0.5)	99 (0.4)	1%
Chronic lung disease	9171 (19.8)	4620 (20.0)	4551 (19.7)	1%
Dementia	1523 (3.3)	687 (3.0)	836 (3.6)	3%
Depression	5314 (11.5)	2550 (11.0)	2764 (11.9)	3%
Hospitalized bleed	1263 (2.7)	642 (2.8)	621 (2.7)	1%
Smoking status				
Non-smoker	33,727 (72.9)	16,007 (69.2)	17,720 (76.6)	**17%**
Former smoker	11,013 (23.8)	6326 (27.3)	4687 (20.3)	**16%**
Smoker	1546 (3.3)	811 (3.5)	735 (3.2)	2%
Health status measures in the one year prior				
Body mass index, mg/kg^2				
<18.5	442 (1.0)	249 (1.1)	193 (0.8)	3%
18.5-<25	8592 (18.6)	4915 (21.2)	3677 (15.9)	**14%**
25-<30	11,532 (24.9)	6461 (27.9)	5071 (21.9)	**14%**
30-<40	8603 (18.6)	4649 (20.1)	3954 (17.1)	8%
≥40	571 (1.2)	309 (1.3)	262 (1.1)	2%
Unknown	16,546 (35.7)	6561 (28.3)	9985 (43.1)	**31%**
Systolic blood pressure, mmHg				
<120	4456 (9.6)	2353 (10.2)	2103 (9.1)	4%
120-<130	4485 (9.7)	2380 (10.3)	2105 (9.1)	4%
130-<140	7624 (16.5)	4046 (17.5)	3578 (15.5)	5%
140-<160	10,287 (22.2)	6070 (26.2)	4217 (18.2)	**19%**
160-<180	2903 (6.3)	1690 (7.3)	1213 (5.2)	9%
≥180	631 (1.4)	369 (1.6)	262 (1.1)	4%
Unknown	15,900 (34.4)	6236 (26.9)	9664 (41.8)	**32%**
Prescription characteristics				
Prescription class, No. (%)				
Angiotensin converting enzyme (ACE) inhibitor	29,247 (63.2)	14,507 (62.7)	14,740 (63.7)	2%
ACE inhibitor / thiazide combination	10,091 (21.8)	5211 (22.5)	4880 (21.1)	3%
Angiotensin receptor blocker (ARB)	6557 (14.2)	3244 (14.0)	3313 (14.3)	1%
ARB / thiazide combination	391 (0.8)	182 (0.8)	209 (0.9)	1%
Percentage of maximum daily dose				
Mean (SD)	28.7 (22.4)	25.5 (18.4)	31.9 (25.4)	**29%**
Median (IQR)	25.0 (12.5-25.0)	25.0 (12.5-25.0)	25.0 (12.5-50.0)	
Range	1.3-100.0	1.3-100.0	1.6-100.0	
Baseline medication use in the 120 days prior to or on prescription date, n (%)				
Beta blocker	19,668 (42.5)	10,151 (43.9)	9517 (41.1)	6%
Calcium channel blocker	8951 (19.3)	4610 (19.9)	4341 (18.8)	3%
Loop diuretic	4762 (10.3)	2462 (10.6)	2300 (9.9)	2%
Thiazide diuretic	17,766 (38.4)	8990 (38.8)	8776 (37.9)	2%

Potassium-sparing diuretic	444 (1.0)	217 (0.9)	227 (1.0)	1%
Alpha blocker	4612 (10.0)	2309 (10.0)	2303 (10.0)	<1%
Any anti-hypertensive agent	35,021 (75.7)	17,751 (76.7)	17,270 (74.6)	5%
Nitrates	1564 (3.4)	790 (3.4)	774 (3.3)	1%
Antiarrhythmic drug	587 (1.3)	333 (1.4)	254 (1.1)	3%
Statin	24,189 (52.3)	12,255 (53.0)	11,934 (51.6)	3%
Other lipid-lowering agent	1663 (3.6)	886 (3.8)	777 (3.4)	2%
Non-aspirin antiplatelet agent	1836 (4.0)	941 (4.1)	895 (3.9)	1%
Low molecular weight heparin	263 (0.6)	151 (0.7)	112 (0.5)	3%
Non-steroidal anti-inflammatory drug	5860 (12.7)	2965 (12.8)	2895 (12.5)	1%
Diabetic therapy	4794 (10.4)	2350 (10.2)	2444 (10.6)	1%
Baseline laboratory values in the one year prior				
Estimated glomerular filtration rate (eGFR), mL/min/1.73 m^2				
Mean (SD)	67.0 (16.9)	67.1 (17.0)	67.0 (16.9)	<1%
Median (IQR)	68.0 (55.0-80.7)	68.0 (55.0-80.7)	68.0 (54.9-80.7)	
Range	9.5-119.5	9.5-119.5	11.0-118.6	
eGFR, No. (%), mL/min/1.73 m^2				
60-150	30,631 (66.2)	15,326 (66.2)	15,305 (66.1)	<1%
45-<60	10,496 (22.7)	5241 (22.6)	5255 (22.7)	<1%
30-<45	4383 (9.5)	2193 (9.5)	2190 (9.5)	<1%
15-<30	765 (1.7)	378 (1.6)	387 (1.7)	1%
<15	11 (0.0)	6 (0.0)	5 (0.0)	<1%
Serum creatinine, mg/dL				
Mean (SD)	1.0 (0.3)	1.0 (0.3)	1.0 (0.3)	<1%
Median (IQR)	0.9 (0.8-1.1)	0.9 (0.8-1.1)	0.9 (0.8-1.1)	
Range	0.3-5.6	0.4-5.6	0.3-4.3	
Time from baseline serum creatinine to prescription date, days				
Mean (SD)	101 (103)	112 (106)	90 (97)	**0.21**
Median (IQR)	64 (13-169)	77 (17-187)	52 (9-148)	
Range	0-365	0-365	0-365	
Serum potassium, mEq/L				
Mean (SD)	4.3 (0.4)	4.3 (0.4)	4.3 (0.4)	<1%
Median (IQR)	4.3 (4.1-4.6)	4.3 (4.1-4.6)	4.3 (4.1-4.6)	
Range	2.5-5.4	2.5-5.4	2.7-5.4	
Serum potassium, No. (%), mEq/L				
<5.0	43,452 (93.9)	21,723 (93.9)	21,729 (93.9)	<1%
5.0-5.5	2834 (6.1)	1421 (6.1)	1413 (6.1)	<1%
Time from baseline potassium to prescription date, days				
Mean (SD)	110 (107)	120 (110)	99 (102)	**21%**
Median (IQR)	75 (14-186)	91 (19-204)	62 (10-167)	
Range	0-365	0-365	0-365	
Hemoglobin, No. (%), g/L				
≥14	16,014 (34.6)	8084 (34.9)	7930 (34.3)	1%
13.0-<14	9628 (20.8)	4761 (20.6)	4867 (21.0)	1%
12.0-<13	5877 (12.7)	2913 (12.6)	2964 (12.8)	1%
11.0-<12	2473 (5.3)	1232 (5.3)	1241 (5.4)	<1%
10.0-<11	877 (1.9)	458 (2.0)	419 (1.8)	1%

9.0-<10	293 (0.6)	160 (0.7)	133 (0.6)	1%
<9.0	117 (0.3)	75 (0.3)	42 (0.2)	2%
Unknown	11,007 (23.8)	5461 (23.6)	5546 (24.0)	1%
Hemoglobin A1C category, %				
Mean (SD)	6.3 (1.0)	6.3 (1.0)	6.3 (1.0)	<1%
Median (IQR)	6.0 (5.7-6.6)	6.0 (5.7-6.5)	6.0 (5.7-6.6)	
Range	3.5-17.8	4.1-16.8	3.5-17.8	
Unknown, n (%)	11,344 (24.5)	5612 (24.2)	5732 (24.8)	
Urine dipstick protein excretion				
0+	3112 (6.7)	1607 (6.9)	1505 (6.5)	2%
1+	2035 (4.4)	1067 (4.6)	968 (4.2)	2%
2+	797 (1.7)	436 (1.9)	361 (1.6)	2%
3+	209 (0.5)	117 (0.5)	92 (0.4)	1%
Unknown	40,133 (86.7)	19,917 (86.1)	20,216 (87.4)	4%
Baseline healthcare utilization in the one year on and prior to prescription date				
Primary care visits				
Mean (SD)	5.3 (5.4)	5.5 (5.7)	5.0 (4.9)	8%
Median (IQR)	4.0 (2.0-7.0)	4.0 (2.0-7.0)	4.0 (2.0-6.0)	
Range	0.0-103.0	0.0-103.0	0.0-101.0	
Hospitalizations				
Mean (SD)	0.3 (0.7)	0.3 (0.7)	0.3 (0.7)	5%
Median (IQR)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	
Range	0.0-16.0	0.0-14.0	0.0-16.0	
Emergency department visits				
Mean (SD)	0.5 (1.1)	0.5 (1.1)	0.5 (1.1)	3%
Median (IQR)	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.0 (0.0-1.0)	
Range	0.0-38.0	0.0-38.0	0.0-34.0	
Nephrology visits				
Mean (SD)	0.0 (0.4)	0.1 (0.4)	0.0 (0.3)	4%
Median (IQR)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	
Range	0.0-19.0	0.0-19.0	0.0-7.0	

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; KPNC, Kaiser Permanente Northern California; IQR, interquartile range; NSAID, non-steroidal anti-inflammatory drug; SD, standard deviation; Stan. Diff., standardized difference.

Appendix Table 12. Baseline characteristics for patients in the Ontario laboratory catchment area (Ontario cohort only)

Variable	Follow-up tests (N=8910)	No follow-up tests (N=8910)	Stan. Diff.
Demographic characteristics			
Age, year			
Mean (SD)	75.1 (6.9)	75.1 (6.9)	<1%
Median (IQR)	74 (69-80)	74 (69-80)	
Range	66-100	66-98	
Age, No. (%), year			
66-<75	4734 (53.1)	4748 (53.3)	<1%
75-<85	3186 (35.8)	3166 (35.5)	1%
85+	990 (11.1)	996 (11.2)	<1%
Gender			
Women	4593 (51.5)	4743 (53.2)	3%
Men	4317 (48.5)	4167 (46.8)	3%
Income quintile, No. (%)*			
1 (lowest)	1556 (17.5)	1650 (18.5)	3%
2	1773 (19.9)	1760 (19.8)	<1%
3	1835 (20.6)	1828 (20.5)	<1%
4	1837 (20.6)	1838 (20.6)	<1%
5 (highest)	1909 (21.4)	1834 (20.6)	2%
Rural residence, No. (%)†	604 (6.8)	681 (7.6)	3%
Local Health Integration Network, No. (%)			
1	12 (0.1)	16 (0.2)	1%
2 or 3	1678 (18.8)	1549 (17.4)	4%
5	561 (6.3)	584 (6.6)	1%
6	1168 (13.1)	1171 (13.1)	<1%
7	987 (11.1)	894 (10.0)	3%
8	1622 (18.2)	1612 (18.1)	<1%
9	2299 (25.8)	2385 (26.8)	2%
10	0 (0.0)	62 (0.7)	**12%**
11	11 (0.1)	24 (0.3)	3%
12	44 (0.5)	77 (0.9)	5%
13 or 14	528 (5.9)	536 (6.0)	1%
Time from prescription date to index date, days			
Mean (SD)	11.0 (8.4)	12.6 (8.6)	**19%**
Median (IQR)	9 (4-17)	11 (5-19)	
Range	1-30	1-30	
Year of prescription date, No. (%)			
2007 or 2008	45 (0.5)	40 (0.4)	1%
2009	91 (1.0)	79 (0.9)	1%
2010	131 (1.5)	113 (1.3)	2%
2011	150 (1.7)	126 (1.4)	2%
2012	228 (2.6)	231 (2.6)	<1%
2013	750 (8.4)	625 (7.0)	5%
2014	3606 (40.5)	3123 (35.1)	**11%**
2015	3909 (43.9)	4573 (51.3)	**15%**
Medical history in the 5 years prior to or on prescription date (unless otherwise specified), No.			

Variable	Follow-up tests (N=8910)	No follow-up tests (N=8910)	Stan. Diff.
(%)			
Johns Hopkins ADG score in the 2 years prior to or on prescription date			
Mean (SD)	7.8 (3.8)	7.8 (3.8)	2%
Median (IQR)	7 (5-10)	7 (5-10)	
Range	0-22	0-24	
Charlson comorbidity score			
0	6093 (68.4)	6231 (69.9)	3%
1	1117 (12.5)	1177 (13.2)	2%
2	874 (9.8)	771 (8.7)	4%
3	826 (9.3)	731 (8.2)	4%
Acute myocardial infarction	248 (2.8)	241 (2.7)	<1%
Heart failure	1034 (11.6)	997 (11.2)	1%
Ischemic stroke or transient ischemic attack	368 (4.1)	385 (4.3)	1%
Peripheral arterial disease	110 (1.2)	119 (1.3)	1%
Mitral and/or aortic valvular disease	145 (1.6)	155 (1.7)	1%
Atrial flutter or fibrillation	575 (6.5)	590 (6.6)	1%
Ventricular tachycardia or fibrillation	155 (1.7)	167 (1.8)	1%
Coronary artery bypass graft surgery	158 (1.8)	152 (1.7)	1%
Percutaneous coronary intervention	292 (3.3)	283 (3.2)	1%
Diabetes mellitus	3757 (42.2)	3811 (42.8)	1%
Hypertension	7551 (84.7)	7521 (84.4)	1%
Dyslipidemia	2841 (31.9)	2959 (33.2)	3%
Hyperthyroidism	158 (1.8)	151 (1.7)	1%
Hypothyroidism	902 (10.1)	880 (9.9)	1%
Cancer	1435 (16.1)	1214 (13.6)	7%
Cirrhosis	106 (1.2)	82 (0.9)	3%
Chronic lung disease	1930 (21.7)	1926 (21.6)	<1%
Dementia	802 (9.0)	787 (8.8)	1%
Depression	140 (1.6)	141 (1.6)	<1%
Hospitalized bleed	914 (10.3)	969 (10.9)	2%
Prescription characteristics			
Prescription class, No. (%)			
ACE inhibitor	5149 (57.8)	4,867 (54.6)	6%
ACE inhibitor/ thiazide combination	494 (5.5)	512 (5.7)	1%
ARB	2550 (28.6)	2,780 (31.2)	6%
ARB/ thiazide combination	717 (8.0)	751 (8.4)	1%
Percentage of maximum daily dose			
Mean (SD)	51.8 (28.5)	54.3 (29.3)	9%
Median (IQR)	50 (25-50)	50 (25-100)	
Range	5-100	5-100	
Baseline medication use in the 120 days prior to or on prescription date, n (%)			
Beta blocker	2650 (29.7)	2607 (29.3)	1%

Variable	Follow-up tests (N=8910)	No follow-up tests (N=8910)	Stan. Diff.
Calcium channel blocker	2673 (30.0)	2695 (30.2)	1%
Loop diuretic	932 (10.5)	759 (8.5)	7%
Thiazide diuretic	2610 (29.3)	2544 (28.6)	2%
Potassium-sparing diuretic	377 (4.2)	310 (3.5)	4%
Alpha blocker	222 (2.5)	202 (2.3)	1%
Any anti-hypertensive agent	5910 (66.3)	5840 (65.5)	2%
Nitrates	432 (4.8)	354 (4.0)	4%
Antiarrhythmic drug	125 (1.4)	110 (1.2)	1%
Statin	4986 (56.0)	5110 (57.4)	3%
Other lipid-lowering agent	597 (6.7)	639 (7.2)	2%
Non-aspirin antiplatelet agent	566 (6.4)	542 (6.1)	1%
Low molecular weight heparin	37 (0.4)	16 (0.2)	4%
NSAID	780 (8.8)	844 (9.5)	2%
Diabetic therapy	2388 (26.8)	2476 (27.8)	2%
Baseline laboratory values in the one year prior to or on prescription date			
eGFR, mL/min/1.73 m^2			
Mean (SD)	69.2 (17.9)	69.2 (17.8)	<1%
Median (IQR)	72 (57-84)	71 (57-84)	
Range	9.8-108.0	10.4-108.4	
eGFR, No. (%), mL/min/1.73 m^2			
60-150	6218 (69.8)	6218 (69.8)	<1%
45-59	1724 (19.3)	1724 (19.3)	<1%
30-44	763 (8.6)	771 (8.7)	1%
<30	205 (2.3)	197 (2.2)	1%
Serum creatinine, mg/dL			
Mean (SD)	1.0 (0.3)	1.0 (0.3)	2%
Median (IQR)	1 (1-1)	1 (1-1)	
Range	0.37-5.09	0.38-4.12	
Time from baseline serum creatinine to prescription date, days			
Mean (SD)	133 (115)	108 (101)	**23%**
Median (IQR)	100 (26-225)	74 (21-183)	
Range	0-365	0-365	
Serum potassium, mEq/L			
Mean (SD)	4.3 (0.4)	4.4 (0.4)	4%
Median (IQR)	4 (4-5)	4 (4-5)	
Range	2.8-5.5	2.8-5.5	
Serum potassium category, No. (%),mEq/L			
< 5.0	8221 (92.3)	8221 (92.3)	2%
5.0-5.5	689 (7.7)	689 (7.7)	2%
Time from baseline potassium to prescription date, days			
Mean (SD)	141 (116)	119 (105)	**20%**
Median (IQR)	116 (29-236)	89 (24-203)	
Range	0-365	0-365	
Hemoglobin category, No. (%), g/L			
≥14	3182 (35.7)	3293 (37.0)	3%
13.0-13.9	2226 (25.0)	2260 (25.4)	1%
12.0-12.9	1624 (18.2)	1601 (18.0	1%
11.0-11.9	805 (9.0)	825 (9.3)	1%
10.0-10.9	334 (3.7)	334 (3.7)	<1%

Variable	Follow-up tests (N=8910)	No follow-up tests (N=8910)	Stan. Diff.
9.0-9.9	178 (2.0)	140 (1.6)	3%
<9.0	62 (0.7)	39 (0.4)	3%
Unknown	499 (5.6)	418 (4.7)	4%
Hemoglobin A1C category, %			
Mean (SD)	6.4 (1.1)	6.4 (1.1)	4%
Median (IQR)	6.1 (5.7-6.8)	6.1 (5.7-6.8)	
Range	4.0-15.0	4.2-16.1	
Unknown, n (%)	2546 (28.6)	2225 (25.0)	4%
Albumin-to-creatinine ratio, No. (%), mg/mmol			
Undetectable	681 (7.6)	682 (7.7)	<1%
< 30	1529 (17.2)	1452 (16.3)	2%
30-300	824 (9.2)	793 (8.9)	1%
>300	234 (2.6)	226 (2.5)	1%
Unknown	5,642 (63.3)	5,757 (64.6)	3%
Baseline healthcare utilization in the one year on and prior to prescription date			
Primary care visits			
Mean (SD)	8.5 (9.2)	8.4 (8.3)	2%
Median (IQR)	6 (4-10)	6 (4-10)	
Range	0-200	0-140	
Hospitalizations			
Mean (SD)	0.2 (0.6)	0.2 (0.6)	5%
Median (IQR)	0 (0-0)	0 (0-0)	
Range	0-6	0-9	
Emergency department visits			
Mean (SD)	0.7 (1.3)	0.6 (1.3)	4%
Median (IQR)	0 (0-1)	0 (0-1)	
Range	0-21	0-20	
Nephrology visits			
Mean (SD)	0.2 (1.0)	0.2 (0.8)	2%
Median (IQR)	0 (0-0)	0 (0-0)	
Range	0-30	0-21	
Prescribing physician characteristics			
Physician age, years			
Mean (SD)	54.7 (10.4)	56.2 (10.3)	**14%**
Median (IQR)	55 (47-62)	56 (49-64)	
Range	29-90	31-86	
Unknown, n (%)	1824 (20.5)	1626 (18.2)	6%
Physician gender, No. (%)			
Women	2213 (24.8)	2018 (22.6)	5%
Men	4873 (54.7)	5266 (59.1)	9%
Unknown	1824 (20.5)	1626 (18.2)	6%
Physician rural practice location, No. (%)	364 (4.1)	413 (4.6)	3%
Unknown	1824 (20.5)	1626 (18.2)	6%
Physician specialty, No. (%)			
Nephrologist	195 (2.2)	171 (1.9)	2%
Primary care	5751 (64.5)	6004 (67.4)	6%
Cardiologist	498 (5.6)	499 (5.6)	<1%
Other	642 (7.2)	610 (6.8)	1%

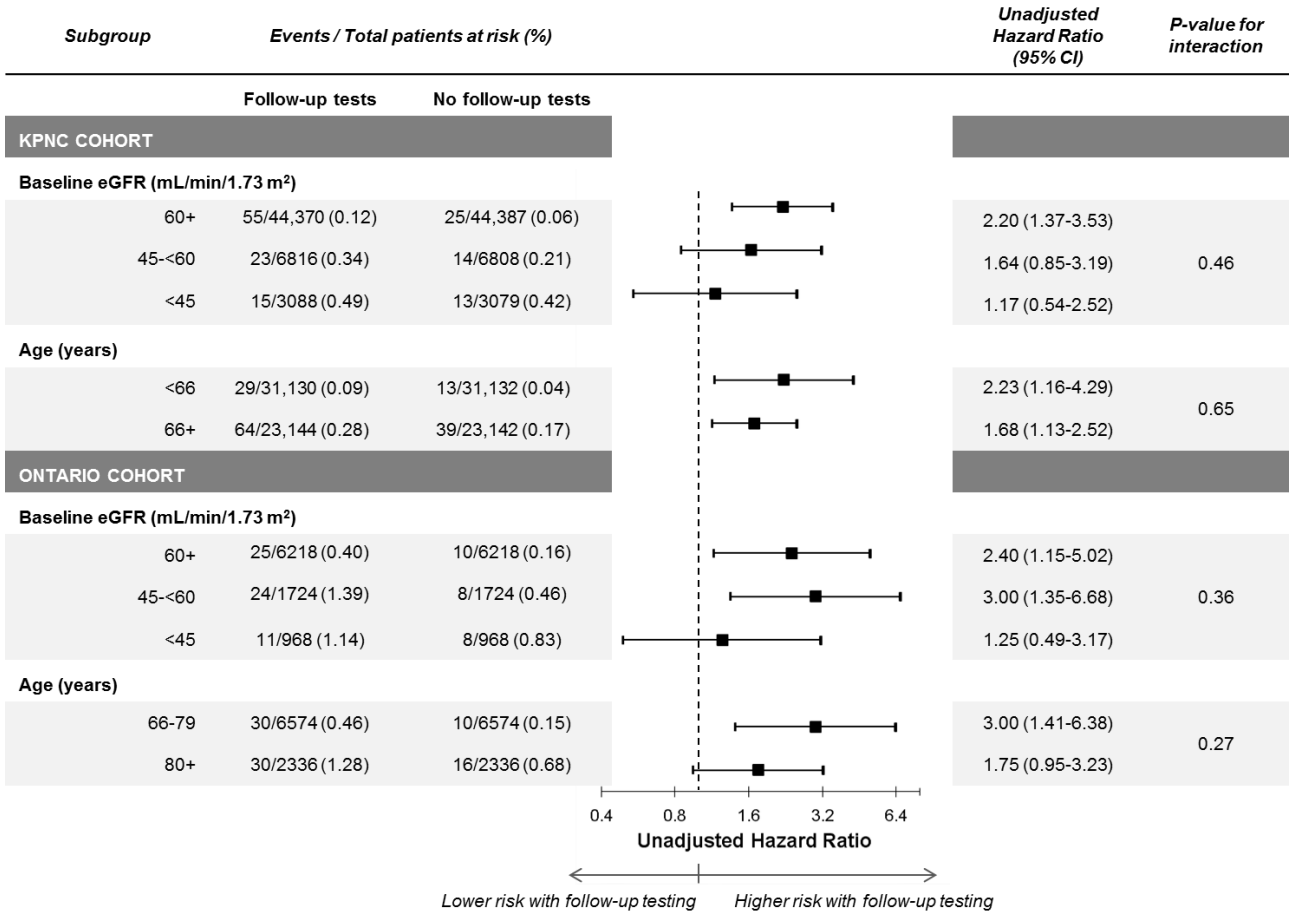
Variable	Follow-up tests (N=8910)	No follow-up tests (N=8910)	Stan. Diff.
Unknown	1824 (20.5)	1626 (18.2)	6%
Canadian medical school graduate, No. (%)	5060 (56.8)	5086 (57.1)	1%
Unknown	1824 (20.5)	1626 (18.2)	6%
Time since graduation, years			
Mean (SD)	28.5 (10.8)	30.0 (10.6)	**13%**
Median (IQR)	29 (21-36)	30 (22-38)	
Range	3-65	3-62	
Unknown, n (%)	1824 (20.5)	1626 (18.2)	6%
Primary care provider type, No. (%)			
Family Health Organization	2930 (32.9)	2814 (31.6)	3%
Family Health Group	3049 (34.2)	3237 (36.3)	4%
Family Health Network	181 (2.0)	183 (2.1)	<1%
Comprehensive Care Model	329 (3.7)	320 (3.6)	1%
Other	100 (1.1)	124 (1.4)	3%
Unknown	2321 (26.0)	2232 (25.1)	2%

Abbreviations: ACE, angiotensin converting enzyme; ADG, Aggregated Diagnostic Group; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; IQR, interquartile range; NSAID, non-steroidal anti-inflammatory drug; SD, standard deviation; Stan. Diff., standardized difference.

* Missing imputed into the middle (third) income quintile.

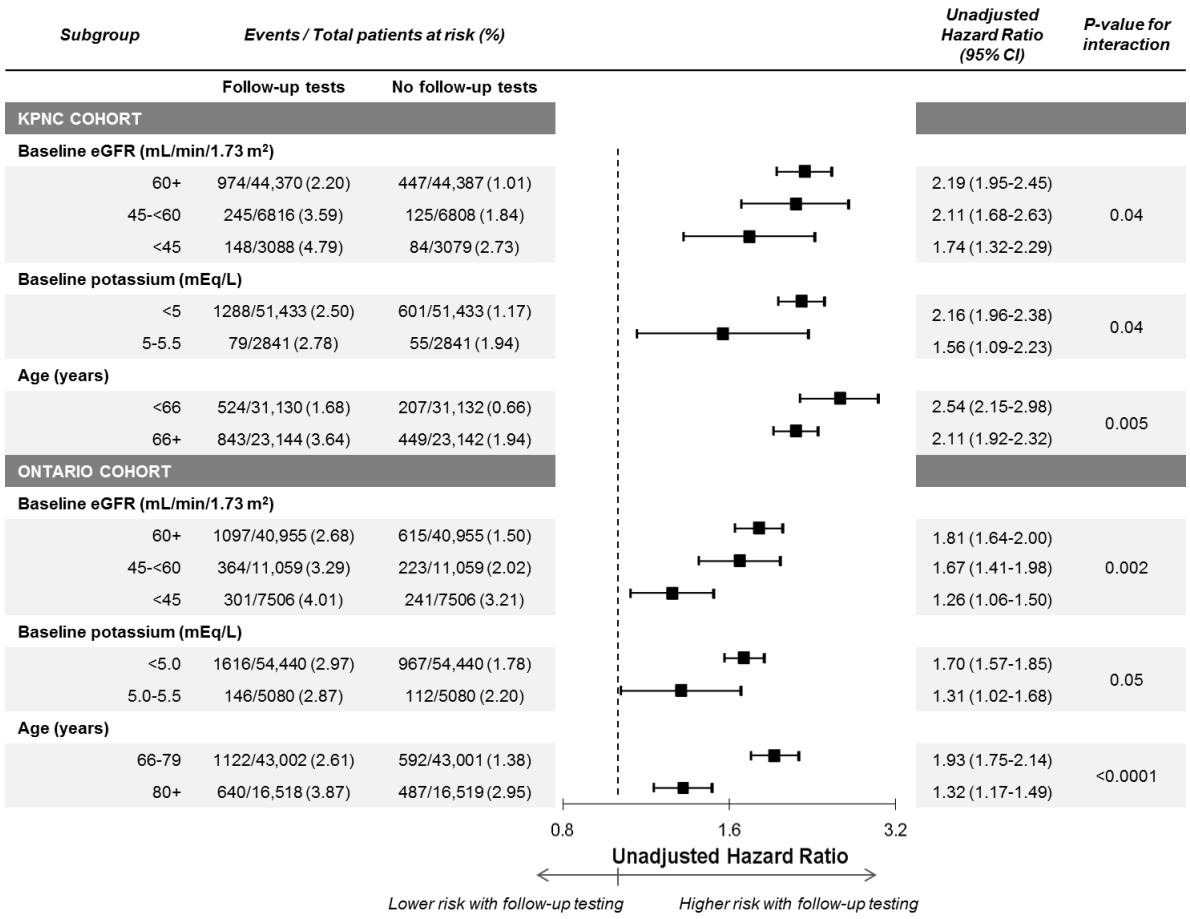
† Missing categorized as not rural.

Appendix Figure 1. Subgroup analyses for the outcome of hospitalization with acute kidney injury comparing patients who received follow-up serum creatinine and potassium tests to propensity-matched patients without follow-up tests



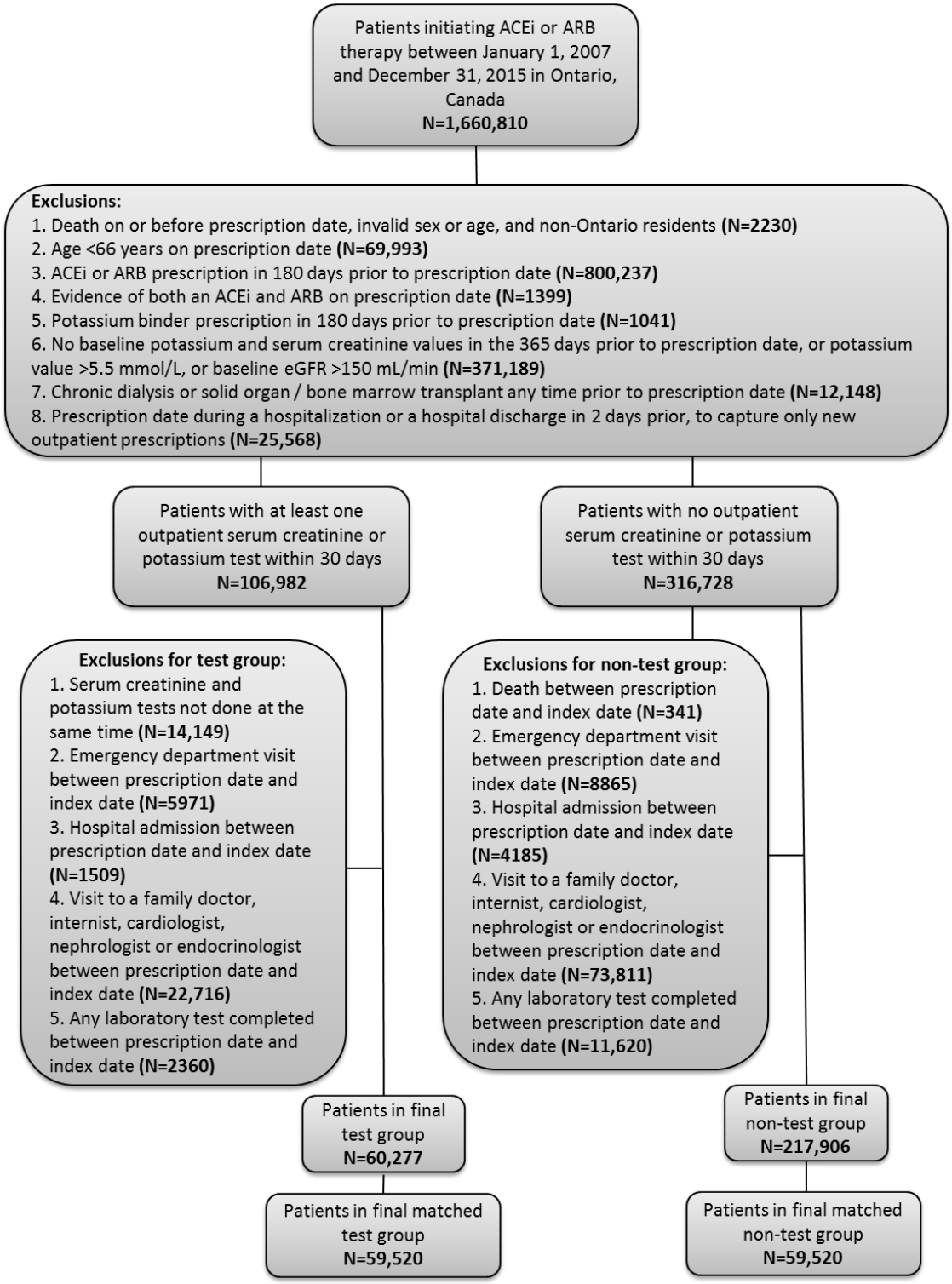
Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; KPNC, Kaiser Permanente Northern California.

Appendix Figure 2. Subgroup analyses for the outcome of all-cause hospitalization comparing patients who received follow-up serum creatinine and potassium tests to propensity-matched patients without follow-up tests



Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; KPNC, Kaiser Permanente Northern California.

Appendix Figure 3. Cohort assembly for patients in the Ontario study



Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ED, emergency department; eGFR, estimated glomerular filtration rate.

Appendix Methods 1. Differences between the Kaiser Permanente Northern California and Ontario cohort assembly

For the Ontario cohort assembly, we also excluded patients who were discharged from the hospital on the prescription date or in the two days prior. We did this to ensure that we captured only new outpatient prescriptions, since patients who initiate treatment in hospital fill ongoing prescriptions on the hospital discharge date or the day after.

In the Ontario cohort, when we identified patients who received laboratory serum creatinine and potassium monitoring, we did not exclude patients from the cohort if they only had one test but not the other; rather, we removed these patients from the test group but still considered them for inclusion in the non-test group. Similarly, we did not exclude patients considered for the test group who had healthcare encounters between the index and tests dates from the overall cohort. These patients were included in the non-test group. After we randomly assigned index dates (i.e., "test dates") to the non-test group, we performed the same exclusions (death or health care encounters between prescription and index dates) and these patients would have been removed from the cohort at this stage depending on the date of their randomly assigned index date. We made this change in the protocol, since we realized that patients in the non-test group in the KPNC cohort, by definition, could not have any laboratory tests in the one to 30 days after the prescription date, even if these tests were after their randomly assigned index date.

Finally, in the Ontario cohort, we initially considered multiple ACEi or ARB prescription dates per person and selected the first eligible record per person after all exclusions were applied.

Appendix Methods 2. Laboratory outcome assessment across Ontario hospitals

Hospitals across Ontario started contributing laboratory data for electronic reporting at different times, so we identified geographic areas across time where residents would most likely present to a hospital with linked laboratory results if they were ill (referred to as the Ontario laboratory catchment area). Therefore, we only assessed the outcomes of hospitalization with acute kidney injury and hyperkalemia among the patients residing in this catchment area.

For the Ontario cohort, in addition to the matching criteria outlined in the manuscript, we also matched on patients residing in the Ontario laboratory catchment area. For baseline characteristics of patients in this catchment area see Appendix Table 12.

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6. CONCLUSIONS

6.1 Summary of Findings

The purpose of this Doctoral thesis was: (1) to identify current quality of care gaps for patients with chronic kidney disease in the primary care setting in Ontario; (2) to understand why some guideline-recommended care practices for chronic kidney disease are not being implemented by primary care providers; (3) and to provide further evidence on whether implementation of guideline-recommended practices is associated with improved patient outcomes. Four separate studies were completed to address these research objectives.

The first study was the largest and most comprehensive population-based study in the world to assess the quality of care for patients with early chronic kidney disease. Among the eleven quality indicators measured,[1] the majority were being implemented in practice. For example, most patients with chronic kidney disease were receiving regular laboratory monitoring for their kidney function. Most patients with chronic kidney disease who should have been receiving an ACEi or an ARB prescription were receiving this treatment. However, there were some care gaps identified. Approximately 75% of patients receiving initial ACEi or ARB treatment did not have their serum creatinine and potassium levels routinely measured in the following 7 to 30 days. Similarly, approximately half of the patients with initial abnormal kidney function test results (eGFR <60 mL/min/1.73m^2 or ACR >3 mg/mmol) were not receiving follow-up laboratory tests to confirm the presence of chronic kidney disease. Furthermore, 35% of patients who should have been receiving statin therapy were not on statins. Finally,

although it is reassuring that 84% of patients were not receiving prescription NSAID therapy for more than 14 days, there were still 16% of patients receiving this treatment. This is concerning since clinical guidelines recommend that patients with chronic kidney disease should avoid long-term use of NSAIDs, since it may lead to further kidney injury. The results from this study provided the motivation for the remaining three studies.

A second qualitative descriptive study was completed to further understand why approximately half of the patients with an initial eGFR <60 mL/min/1.73m^2 were not receiving follow-up laboratory tests, from the perception of primary care providers. In this study, 13 interviews with primary care providers (9 physicians and 4 nurse practitioners) from across Ontario were completed. Nine out of 13 participants were female, the average age was 46 years, and the majority practiced as part of a family health team or group. A number of key enablers and barriers emerged from the data. This study found perceived enablers, including that providers generally know what they should be doing, are motivated to do so, have the tools and resources required to perform the task, and use both the information and tools to make an informed decision on whether or not to order a repeat serum creatinine test. However, some of the barriers identified were that ordering follow-up serum creatinine tests was not always perceived as a priority or as directly influencing patient outcomes, and could be forgotten. Providers also noted that a perceived barrier was patients not going to the laboratory to complete the test. This was the first qualitative study to assess the enablers and barriers to ordering repeat serum creatinine tests to confirm a diagnosis of chronic kidney disease, from the perspective of primary care providers.

The third study was completed to provide further evidence on the impact of NSAID use among all older adults and specifically for patients with chronic kidney disease. The study findings were that NSAID use versus non-use was associated with a higher 30-day risk of acute kidney injury and hyperkalemia, but not all-cause mortality. Presence of chronic kidney disease at baseline did not significantly modify the association between NSAID use and acute kidney injury or hyperkalemia; although, this sub-group analysis had limited statistical power for modest effects. In this study, a prediction model was also created to identify patients most at-risk for acute kidney injury or hyperkalemia based on six predictors: older age, male gender, lower baseline eGFR, higher baseline serum potassium, ACEi or ARB use, or diuretic use. To our knowledge, this large population-based study was the first of its kind to use a cohort design to quantify the absolute risk of acute kidney injury and hyperkalemia with NSAID use. This was also the first study to develop a prediction model to help identify people with the greatest chance of developing these outcomes if they were prescribed NSAIDs. This prediction model is available as an online calculator to assist providers with clinical decision-making in practice.

The aim of the fourth study was to provide further evidence for the recommendation that routine laboratory monitoring should be completed shortly after ACEi or ARB initiation. Two separate community-based cohort studies were completed using data from Ontario, Canada and Kaiser Permanente Northern California. Both studies showed consistent findings that routinely measuring serum creatinine and potassium after ACEi or ARB initiation among older adults was not associated with a

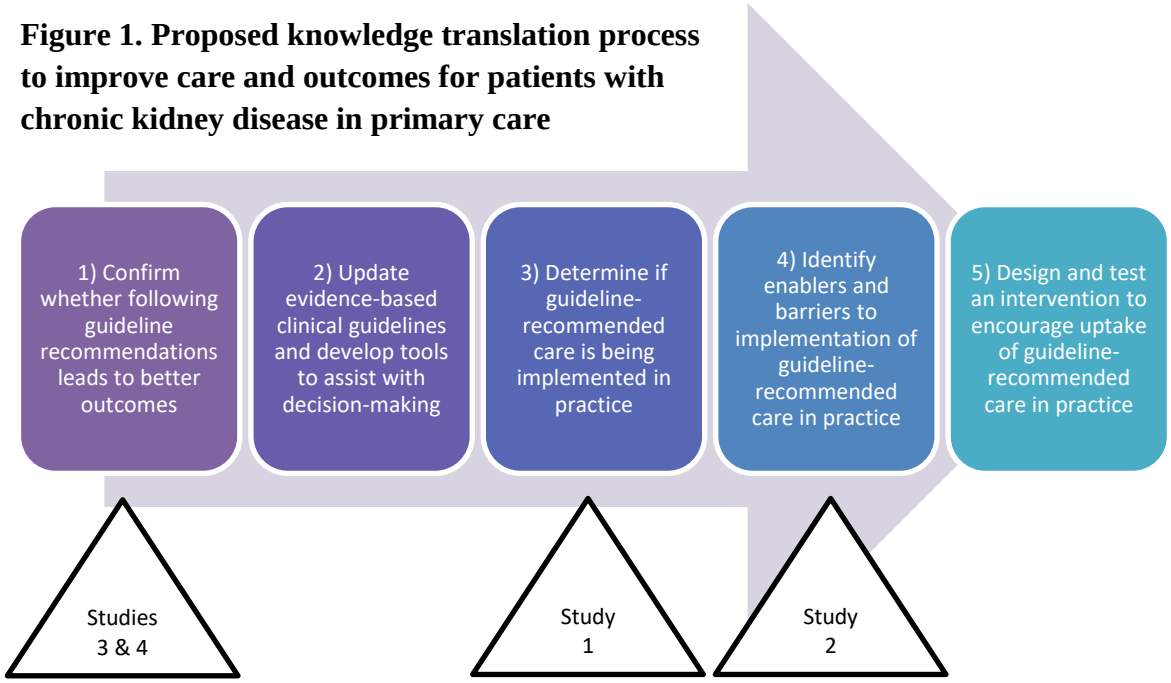
lower risk of all-cause mortality compared to no such measurements. Presence of chronic kidney disease at baseline did not significantly modify the association between routine monitoring and all-cause mortality.

6.2 Study Implications and Future Directions

Confirm whether following guideline recommendations lead to better outcomes

Based on the conclusions of study 4, it is important to take a step back and consider which care indicators for study 1 improve care and prevent adverse outcomes for patients with chronic kidney disease, and thus should be recommended in practice. Ideally, all the indicators examined in study 1 should be critically examined and follow the progression outlined in **Figure 1** below to ensure adequate knowledge translation and performance improvement. This figure was based on components from the knowledge-to-action cycle, specifically creating knowledge (steps 1 and 2), monitoring knowledge use (step 3), assessing barriers and enablers to knowledge use (step 4), and selecting, tailoring, and implementing interventions (step 5).[2] Indicators not found to prevent adverse patient outcomes in step one should not proceed to subsequent steps.

Figure 1. Proposed knowledge translation process to improve care and outcomes for patients with chronic kidney disease in primary care



Update evidence-based clinical guidelines and develop tools to assist with decision-making

The findings from the third and fourth studies can be used to update current guideline recommendations. Many clinical guidelines already include warnings about NSAID use among patients with reduced kidney function. These warnings can be extended to all older adults, and references to the online calculator can help providers and patients to make informed decisions on the risks and benefits of initiating prescription NSAIDs or whether patients should receive serum creatinine and potassium monitoring after NSAID initiation. Referring back to the findings from study one, it is reassuring that 84% of patients with chronic kidney disease were not receiving NSAIDs for more than 14 days; however, there is some room for improvement.

The findings from study 4 suggest that recommendations about routine monitoring following ACEi and ARB prescriptions may be overstated, and this practice may not be necessary for all patients. Risk calculators can also be useful in this scenario to identify patients who may benefit most from routine monitoring. A prediction model for risk of hyperkalemia has already been developed and externally validated.[3] Future research should focus on developing and validating models that predict risk of either acute kidney injury or hyperkalemia (similar to the model developed to predict risk among NSAID users in study three). This may be more useful than models predicting individual outcomes, since it could identify patients who would benefit most from serum creatinine and potassium monitoring. Referring back to the findings from study one where only 25% of patients were receiving routine monitoring after ACEi or ARB initiation, it seems that many providers in Ontario have not been following these recommendations anyway. This is reassuring and suggests that a drastic change in practice is unnecessary.

Identify enablers and barriers to implementation of guideline-recommended care in practice

Study 1 provided an overview of the current quality of care for patients with early chronic kidney disease. It is reassuring that many of the quality of care indicators were frequently being implemented in practice. Following the flow of **Figure 1**, future qualitative research is needed to identify enablers and barriers to some of the other guideline-recommended practices that are less frequently implemented. For instance, there is high quality evidence from clinical trials that statin therapy helps reduce the risk of major

cardiovascular events in patients with chronic kidney disease.[4,5] It is unknown why 35% of patients with chronic kidney disease who should be on statins do not receive them.

Co-design and test a knowledge translation intervention to encourage uptake of guideline-recommended care in practice

Study 2 was conducted to determine why follow-up confirmatory testing was not being completed in about half of the cases. Implications from this qualitative study are that the enablers and barriers responsible for behaviour change are complex and multi-factorial, therefore an intervention to improve this behaviour in practice needs to include many components that address modifiable barriers. First, better evidence is needed to convince providers of the benefits of this practice, since one of the identified barriers perceived by providers was whether or not repeating laboratory tests would actually change the care they provide or the prognosis for the patients (i.e. step 1 of **Figure 1**). Before any further actions are taken to encourage this behaviour in practice, further research should be conducted to determine whether or not repeating laboratory tests, and thus confirming a diagnosis of chronic kidney disease, reduces adverse outcomes in patients with suspected chronic kidney disease. An intervention could then address some of the modifiable barriers, for example, effective communication of this evidence to providers could address the barrier of providers perceiving this as low priority. An intervention that uses reminders / prompts within the electronic medical record and support staff to help with patient follow-up can address these enablers. Future research is also warranted that incorporates the patient's perspective regarding the factors that influence completing laboratory tests. We can then engage healthcare providers and patients and their

caregivers to co-design an intervention to address the identified enablers and barriers to optimize care outcomes.

6.3 Concluding Remarks

This research makes an important contribution to the existing knowledge base regarding chronic kidney disease. There is now a better understanding of the overall quality of care for patients with early chronic kidney disease in Ontario primary care, and areas for improvement have been identified. Potential solutions to help improve the practice of ordering confirmatory tests for chronic kidney disease can be developed and tested, informed by the findings of the qualitative study in this thesis. Furthermore, the evidence behind the recommendations for avoiding NSAIDs for patients with chronic kidney disease has been strengthened and can also be extended to all older adults. Finally, it was demonstrated that the practice of ordering routine laboratory tests after ACEi or ARB initiation for all older adults does not prevent adverse outcomes.

6.4 References

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