9-27-2023 9:30 AM

Fracture Prediction and Prevention in Individuals with Chronic Kidney Disease

Andrea C.J. Cowan, *Western University*

Supervisor: Garg, Amit X, *The University of Western Ontario*

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

Abstract

Patients with chronic kidney disease (CKD) face increased fracture risk yet our understanding and management of this risk remains poor. We conducted three studies using retrospective cohort analysis in Ontario, Canada. We developed a 3-year fracture prediction model for patients receiving dialysis. Secondly, we contrasted fracture rates among patients on SGLT2i or DPP4i medications, stratified by kidney function. Lastly, we examined hypocalcemia incidence post-denosumab prescription, stratified by kidney function.

Findings: The fracture risk tool, incorporating demographic and lab data, performed well (AUC 0.72). SGLT2i did not elevate fracture risk vs. DPP4i (HR 0.95 [95% CI 0.79,1.13]). In those prescribed denosumab, hypocalcemia occurred in 0.6% overall but increased to 24.1% in those with eGFR<15 ml/min/1.73m^2. These studies contribute to our understanding of the causes and prediction of fractures in patients with CKD. Further validation of the risk score and research into the efficacy of denosumab and management of hypocalcemia are warranted.

Keywords

CKD, fracture, antiresorptive, risk prediction

Summary for Lay Audience

People with chronic kidney disease are at higher risk of breaking a bone than people with normal kidney function. However, we do not have an easy way of predicting those people with the highest risk so that they can receive treatments or be included in studies. Furthermore, once a person is identified as being at a high risk of breaking a bone, the treatments we have available may have side effects.

We conducted three studies to help answer questions in this area. First, we developed a calculator that will predict the 1- and 3-year risk of breaking a bone for a person receiving dialysis, based on information that is already collected as a part of dialysis care. This calculator did a good job of separating those who will have a fracture and those who will not particularly over the next year.

Then, we examined the effect that a group of diabetes medications called sodium glucose cotransporter-2 inhibitors (SGLT2i) has on the risk of fracture, as some studies have suggested they may increase the risk. We found that SGLT2i were not associated with an increased risk of fracture compared to another group of commonly used diabetes medication called dipeptidyl peptidase 4 inhibitors. This risk did not change when examined over the spectrum of kidney function.

Finally, we looked at the risk of low blood calcium after using a medication called denosumab which is commonly used to decrease the risk of fracture but has been associated with case reports of low blood calcium. We found that although the number of people who had low calcium levels was low, (0.6% of the total group) this risk increased as kidney function decreased. In the group with the lowest level of kidney function, (those on or approaching dialysis) 24% had a measured low calcium level.

The intersection between bone disease, fractures and chronic kidney disease is an understudied one. These three studies help to improve the prediction and prevention of fractures in this population.

Co-Authorship Statement

Under the supervision of Amit Garg, Andrea Cowan played a substantial role in the included manuscripts. Andrea was involved in the conception and design of all studies as well as drafting the protocol for the first study. She also played a primary role in the interpretation of the results of all three studies in addition to performing the analysis for the first study. Finally, she drafted and revised all manuscripts.

A number of co-authors made contributions to the included manuscripts. For the study entitled "Fracture Risk Prediction in Patients Receiving Dialysis", co-authors Yuguang Kang and Stephanie Dixon contributed to the design of the study, acquired the data, advised on the statistical analysis and revised the manuscript critically for its content. Nivethika Jeyakumar contributed to the design of the study and revised the manuscript critically. Kristin Clemens and Amit Garg helped to develop the concept for the study, aided in its interpretation and critically revised the manuscript.

For the study entitled "Fracture Risk of Sodium Glucose Cotransporter-2 Inhibitors in Chronic Kidney Disease", Nivethika Jeyakumar contributed to the design of the study and the creation of the protocol as well as revising the manuscript. Yuguang Kang and Stephanie Dixon contributed to the design of the study, acquired the data and performed the statistical analysis as well as revising the manuscript. Kyla Naylor contributed to the study design and reviewed the manuscript. Matthew Weir, Kristin Clemens and Amit Garg helped to develop the concept for the study, aided in its interpretation and critically revised the manuscript.

For the study entitled "Hypocalcemia risk of denosumab across the spectrum of kidney disease: A population-based cohort study", Nivethika Jeyakumaar contributed to the design of the study and the creation of the protocol as well as revising the manuscript. Eric McArthur contributed to the design of the study, acquired the data and performed the statistical analysis as well as revising the manuscript. Kristin Clemens, Amit Garg and Samuel Silver helped to develop the concept for the study, aided in its interpretation and critically revised the manuscript. Jaime Fleet, Tharsan Kanagalingam, Igor Karp, Tayyab

Khan, Flory Tsobo Muanda, Danielle Nash, Jenny Thain and Matthew Weir all helped to develop the study as well as revising the manuscript for content.

Acknowledgements

I would like to thank Dr. Amit Garg for his support, guidance and mentorship over the last 7 years. I would also like thank my thesis committee: Dr. Kristin Clemens for her clinical guidance, insight; Stephanie Dixon for her very patient support during statistical analysis and Jessica Sontrop for her methodologic insight and manuscript review. Additionally, I would like to thank Yuguang Kang Eric McArthur and Nivethika Jeyakumar for their guidance and support in the planning and execution of these three studies. Finally, thank you to all of my co-authors: Matthew Weir, Kyla Naylor, Danielle Nash, Samuel Silver, Tharsan Kanagalingam, Igor Karp, Jaime Fleet, Tayyab Khan, Flory Tsobo Muanda and Jenny Thain.

Table of Contents

List of Tables

List of Figures

List of Appendices

List of Abbreviations

CKD = chronic kidney disease

CKD-MBD = chronic kidney disease-mineral bone disease

eGFR = estimated glomerular filtration rate

CI = confidence interval

FRAX = fracture risk assessment tool

BMD = bone mineral density

HR = hazard ratio

wHR = weighted hazard ratio

PTH = parathyroid hormone

KDIGO = Kidney Disease Improving Global Outcomes

SGLT-2i =. sodium glucose cotransporter-1 inhibitor

AUC = area under receiver operating curve

bsALP =. bone specific alkaline phosphatase

OSTA = Osteoporosis Self Assessment Tool for Asians

TRIPOD = Transparent reporting of a multivariable prediction model for individual prognosis of diagnosis

CIHI-DAD = Canadian Institute for Health Information Discharge Abstract Database

CIHI-NACRS = Canadian Institute for Health Information National Ambulatory Care Reporting System

ODB = Ontario Drug Benefit

OLIS = Ontario Lab Information System

FCS = fully conditional specification

AIC = Akaike Information Criteria

BIC = Bayesian Information Criteria

SD = standard deviation

DPP-4i = dipeptidyl peptidase-4 inhibitor

RECORD-PE = Reporting of studies Conducted using Observational Routinely collected health Data for PharmacoEpidemiology

ATT = average treatment effects for the treated

IQR = interquartile range

RANKL = Receptor activator of Nuclear Factor Kappaβ Ligand

ICD-10 = International classification of diseases 10

SSRI = selective serotonin reuptake inhibitor

Preface

All work for this thesis was conducted at ICES Western.

The included study “Fracture Risk of Sodium-Glucose Cotransporter-2 Inhibitors in Chronic Kidney Disease” was previously published in the Clinical Journal of the American Society of Nephrology (Andrea Cowan, Nivethika Jeyakumar, Yuguang Kang, Stephanie N Dixon, Amit X Garg, Kyla Naylor, Matthew A Weir, Kristin K Clemens. 2022; 17(6):835-842. doi:10.2215/CJN.16171221)

The included study “Hypocalcemia Risk of Denosumab Across the Spectrum of Kidney Disease: A Population-Based Cohort Study” was previously published in the Journal of Bone and Mineral Research. (Andrea Cowan, Nivethika Jeyakumar, Eric McArthur, Jamie L Fleet, Tharsan Kanagalingam, Igor Karp, Tayyab Khan, Flory Tsobo Muanda, Danielle M Nash, Samuel A Silver, Jenny Thain, Matthew A Weir, Amit X Garg and Kristin K Clemens. Published online April 9, 2023. doi:10.1002/jbmr.4804

Chapter 1

1 Introduction

1.1 What are Fragility Fractures?

Fragility fractures are broken bones that occur with minimal force, such as a fall from standing height. A fragility fracture indicates suboptimal bone strength and is one of the criteria used to diagnose a patient with osteoporosis. Fragility fractures not only impact patients (e.g., pain, hospital admission and loss of function), but they place a large burden on the health care system; globally, an estimated 178 million fragility fractures occur each year, with a total system cost of $4.3 billion per year in Canada alone.[1,2]

1.2 The link between kidney disease, osteoporosis and fragility fracture

Osteoporosis and chronic kidney disease (CKD) commonly coexist. For example, over one quarter of women in the United States with an osteoporosis diagnosis also meet the criteria for moderate or severe CKD.[3] Furthermore, individuals with CKD have an increased risk of fragility fracture compared to their peers without CKD.[4–6] The reasons for this are multifactorial. As kidney function declines, bone changes may also occur—referred to as CKD-Mineral Bone Disease (CKD-MBD). This is a heterogenous group of conditions characterized by abnormalities in bone density and quality, which are caused by dysregulated calcium and phosphate metabolism that occurs as the result of decreased kidney function.[7,8] CKD-MBD is also commonly characterized by secondary hyperparathyroidism.

In addition to the direct effects of CKD on bone health, CKD disproportionately affects older adults, who are also at higher risk of age-related osteoporotic change. For example, the mean age of patients initiating dialysis in Canada is 64, and those over 65 are over 10 times more likely to be diagnosed with mild CKD compared to those under 65.[9,10] Furthermore, age is a well-established risk factor for fracture in the general population, with the risk of osteoporosis doubling every 5 years between the ages of 40 and 60.[11]

Comorbidities that commonly co-occur with CKD can also increase the risk of fracture. Diabetes, which complicates approximately one quarter of cases of CKD in Canada, is independently associated with a higher risk of fracture through both changes in bone quality and an increase in falls.[10,12–14] Individuals with CKD are also at high risk of low muscle mass and frailty due to poor clearance of metabolic waste, which increases the risk of falls and subsequent fracture.[6,15,16]

Fracture rates in patients with CKD who do not require dialysis

The risk of fracture increases as the estimated glomerular filtration rate (eGFR) falls. Even people with relatively mild CKD (i.e., an estimated glomerular filtration rate [eGFR] 45-59 ml/min/1.73m^2) have an increased risk of fracture compared to those with normal kidney function (i.e., eGFR > 60 ml/min/1.73m^2), with the rates of fracture being 1.3 (95% CI 1.2, 1.4) and 1.4 (95% CI 1.3, 1.5) times higher in men and women over age 65, respectively.[4] This corresponds to 7.3 and 20.5 fractures per 1000 patient-years for men and women with mild CKD.[4] The hazard ratio for hip fracture in those with an eGFR <60 ml/min/1.73m^2 is 1.19 (95% CI 1.07, 1.31), compared to those with normal kidney function.[6] A meta-analysis also showed that individuals with an eGFR of 30-44 ml/min/1.73m^2 and 15-29 ml/min/1.73m^2 had an increased rate of fractures that was 1.7-fold (95% CI 1.6, 1.9) and 2-fold (95% CI 1.9-2.3) higher, respectively, than those with normal kidney function.[6]

Fracture rates in patients receiving dialysis

Compared to individuals with normal kidney function, patients receiving hemodialysis have a 4- to 17-fold increased risk of fracture depending on the cohort studied.[4,5,17–19] This corresponds to rates of 10-26 fractures per 1000 patient-years, and means that 1 in 10 women and 1 in 20 men over the age of 65 will suffer a fracture within their first 3 years on dialysis.[4,17,20,21] Although the absolute fracture rates are highest among older women receiving dialysis, the relative increase in fracture risk is higher for men and younger individuals. For example, women aged 40-49 years receiving dialysis have a 70.8 fold (95% CI 41.3, 113.4) increased risk of fracture, but women aged 80-89 receiving dialysis only have a 2.7 fold (95% CI 2.4, 3.1) increase in fracture when

compared to women with normal kidney function in their respective age groups.[18] In a cohort from Ontario, Canada, men aged 40-65 years receiving dialysis also had a 5.1 fold (95% CI 4.0-6.5) increased risk of fracture compared to men of the same age with normal kidney function, while women aged >65 receiving dialysis only had a 3.1 fold (95% CI 2.8, 3.5) increased fracture risk despite women aged > 65 having the highest absolute incidence rate (46 fractures per 1000 patient-years).[4]

1.3 Outcomes after Fracture

Outcomes in patients with CKD not requiring dialysis

In addition to having an increased risk of fracture, individuals with CKD also face worse outcomes following fracture. Most of the literature focusses on the clinical impact of hip fractures as these are most common. After a hip fracture, the in-hospital mortality for those with CKD is approximately 10%, which is 1.8-fold higher than those without CKD.[22,23] In one study, patients with both CKD and diabetes had a one-year mortality rate of 17% after surgical repair for a hip fracture; this rate is approximately two-times higher than that of individuals with normal kidney function.[24] Similarly, the one-year mortality for individuals with CKD and diabetes who had a proximal humerus fracture was 9%, which is 1.9 times higher than those with normal kidney function.[25] Finally, two studies with long-term follow up after hip fracture (i.e., 5.5-7.3 years) showed those with an eGFR <45 and <30 ml/min/1.73m^2 had double the risk of mortality compared to individuals with normal kidney function.[26,27] Only one small study examined functional outcomes, and showed that only 50% of individuals with CKD who suffered a hip fracture were discharged home, even after a stay at a rehabilitation hospital.[23]

Outcomes in patients receiving dialysis

In patients receiving dialysis who suffer a hip fracture, the 30-day mortality after hip fracture ranges from 6-20%, and one-year mortality ranges from 20-61%.[17,28–31] Compared to those with normal kidney function who fracture their hip, the mortality rates in patients receiving dialysis are 2-3 times higher.[17,28–30] Similarly, the one-year mortality

of those receiving dialysis who have a hip fracture is 2-2.7 times higher than those receiving dialysis who have not had a hip fracture.[17,31]

Information on mobility and function after a fracture in patients receiving dialysis is limited. In a study examining all fracture sites, individuals receiving dialysis admitted for a fracture have a higher risk of in-hospital death than those admitted for other reasons.[32] Of those admitted for hip fracture, 67% were discharged to a skilled nursing facility or inpatient rehabilitation, while only 14% were discharged home.[32]

1.4 Risk Factors for Fracture

Risk Factors for fracture in patients with CKD

Information on CKD-specific risk factors for fracture in the literature is sparse, and difficult to interpret given the significant heterogeneity in individuals with CKD. Bone changes associated with CKD are typically seen with laboratory testing when the eGFR drops below 30 ml/min/1.73m^2.[7] As a result, it is likely that fracture prediction methods used in the general population (e.g., the Fracture Risk Assessment Tool [FRAX], as discussed below), might be most appropriate to use in those with an eGFR >30 ml/min/1.73m^2 where the effect of CKD is minimal. [7]

In the general population, bone mineral density (BMD), whose measurement is similar to an x-ray being taken, is commonly used to identify those with osteoporosis and predict individuals at future risk of fracture. Studies of its ability to predict fracture in individuals with CKD have been limited by primarily cross-sectional design and the heterogeneity of the patients included. They have also been small (82-587 patients) and included few individuals with severe CKD (eGFR <30 ml/min/1.73m^2).[33–36] A meta-analysis of 3 studies including patients with non-dialysis-dependent CKD showed that BMD was significantly higher in those with a history of fracture compared to those without.[37] Three trials included patients with eGFRs ranging from 60 ml/min/1.73m^2 to < 15 ml/min/1.73m^2 (including those on dialysis), two of which were cross-sectional designs and showed the odds ratio for fracture ranged from 1.3-1.9 for a one standard deviation decrease in bone density.[34–36] One prospective study found an increased rate of fracture

(HR 2.74) with a one standard deviation decrease in BMD, but did not find a significant interaction between CKD status and fracture risk.[33]

There is little information about other risk factors for fracture in individuals with CKD beyond those that are commonly used in the general population, such as age, gender, history of fracture, steroid use and smoking.[38] One post-hoc analysis of a large efficacy trial of a diabetes medication examined risk factors for fracture in a group of individuals with mild CKD (eGFR 30-89 ml/min/1.73m^2).[39] A cox proportional hazards model using traditional risk factors (age, sex and previous fractures) performed as well as a predictive model including newer, exploratory risk factors (ethnicity, serum albumin, thyroid hormone use, proton pump inhibitor use, vitamin D therapy or beta blocker use). The addition of CKD-specific risk factors (i.e., urinary protein excretion, serum levels of magnesium, phosphate, calcium, bicarbonate, alkaline phosphatase, sodium, or urate) also did not improve the predictive performance. However, low serum albumin, higher hemoglobin A1c, vitamin D therapy, Asian race and prior cardiovascular events were all independently associated with increased fracture risk.[39] In contrast, a large observational study of routinely collected data from Korea showed that higher urinary protein excretion (as measured by urine dipstick) was associated with a higher rate of fracture (HR 1.58 95% CI 1.07-2.35).[40]

Risk factors for fracture in patients receiving dialysis

As in those in those with CKD, both older age and female sex are well as established as consistently associated with an increased incidence of fractures in patients receiving dialysis.[5,21,41–44] For example in one large study, those older than 65 years had a 3.1-fold increased rate of fracture compared to those under 45, and women had a 1.3-fold increase in fracture rate than men.[41] The evidence for other potential predictors, however, is mixed.

Derangements of parathyroid hormone (PTH) are a hallmark of CKD-MBD. Several studies have shown that PTH level is associated with fracture risk, with either lower PTH conferring a higher risk of fracture[17], or showing a U-shaped relationship with the a PTH between 24 and 57 pmol/L being associated with the lowest risk of fracture.[41,45]

Guidelines suggest targeting a PTH 2-9 times the upper limit of normal to minimize fracture risk, given the potential u-shaped relationship between PTH and CKD-MBD severity.[7] A number of other studies showed no association between PTH and fracture; however, they were limited by either small sample sizes, or modelled PTH linearly, which may mask any relationship if the true risk is u-shaped.[21,42,43,46,47]

Fracture risk also increases with the number of years receiving dialysis (often referred to as *dialysis vintage*) in most studies that examined this as a risk factor.[21,41,44,46,48] One study observed an increased risk of fracture once patients had been receiving dialysis for over 16 years.[18] We found one study which did not find dialysis vintage to be predictive of fracture risk, but this was limited by small sample size.[43] A summary of other potential risk factors for fracture in the literature is shown in table 1.

Table 1.1 Risk Factors for Fracture in Patients Receiving Dialysis

Risk Factor	References	Relationship with Fracture Risk
Age	5,20,21,41–44	Increasing risk with increasing age
Sex	5,18,20,21,41,42,44	Female individuals at higher risk
PTH	17,41,45	Both high and low PTH associated with increased risk of fracture
Dialysis Vintage	18,21,41,44,46,48	Higher fracture risk with longer vintage
Body mass index	21,41,42,49	Higher fracture risk with lower body mass index
Ethnicity	21,41,44	Black individuals have a lower risk of fracture
Diabetes	18,41,43,44	Increased fracture risk in patients with diabetes
History of fracture	20,48	Increased fracture risk in those with a previous fracture

In the general population, measurement of BMD is recommended in all individuals over 65 years of age or those younger who have risk factors for fracture.[50] However, given the differing pathophysiology of fractures in patients with kidney disease, the question arises if BMD can predict fractures in patients with CKD.[50] Study results on the utility of BMD in predicting fracture risk on dialysis have been mixed, but limited by small sample sizes and cross-sectional designs.[43,46,48,51,52] A meta-analysis of 13 studies, primarily including patients receiving dialysis, found that lower BMD at the lumbar spine, femoral neck, 1/3, and ultradistal radius was associated with fracture.[37] As a result of growing evidence, a recommendation to measure BMD only if it would change patient management was added to the 2017 Kidney Disease Improving Global Outcomes (KDIGO) guidelines.[7] Trabecular bone score, which includes an analysis of bone microarchitecture. While this has been shown to improve fracture prediction in those with normal kidney function, the evidence in individuals with CKD or requiring dialysis is heterogenous and limited and it is not currently recommended for routine practice in this population.[53,54]

Medications that increase the risk of fracture

Medications commonly given to patients with kidney disease may also increase the risk of fracture. Glucocorticoids, which are used as immunosuppressants in individuals with glomerulonephritis (the second most common cause of kidney disease requiring dialysis in Canada) are associated with a 1.5-2 fold increased risk of fracture compared to those who have not taken glucocorticoids.[10,55] Similarly, proton pump inhibitors, which are prescribed to individuals with CKD both at higher rates and for longer durations than those without CKD, are associated with an increased risk of fracture compared to non-use across the spectrum of CKD.[56–58] Approximately 50% of patients receiving dialysis are prescribed these medications and their use has been associated with a 1.2-1.4 fold increase in fractures in this population.[59–61] Finally, sodium glucose cotransporter-2 inhibitors (SGLT-2i) (i.e., canagliflozin), which are commonly prescribed to patients with diabetes to lower blood sugar levels, are also commonly prescribed to individuals with CKD for their nephroprotective benefits.[62] However, a large efficacy trial found a higher rate of fractures in those prescribed canagliflozin compared to placebo, which was subsequently confirmed in a meta-analysis.[62,63] Subsequent smaller randomized

controlled trials have shown an increased risk of fracture, decreased bone density or hyperparathyroidism with these medications, but have been limited by short follow up times and small sample sizes.[64–66]

1.5 Preventing fragility fractures in patients with CKD

In patients with CKD who have an eGFR >30 ml/min/1.73m^2, first-line therapies for fracture prevention are typically anti-resorptive therapies such as bisphosphonates or denosumab.[50] However as the eGFR drops below 30 ml/min/1.73m^2, the traditional therapeutic options are limited.

Bisphosphonates

Bisphosphonates, which are renally cleared, are traditionally contraindicated in individuals with advanced kidney disease due to reports of acute kidney injury associated with their use, and concerns about drug accumulation.[67–69] Most of the evidence for bisphosphonates in CKD comes from post-hoc analyses of large efficacy trials, which included small numbers of individuals with an eGFR <30 ml/min/1.73^2. A meta-analysis of trials of risedronate, including 571 patients with an eGFR <30 ml/min/1.73m^2 found similar in improvements in BMD and a similar frequency of adverse events in those with and without CKD.[70] Similarly, a post hoc analysis of a large trial of alendronate including 581 patients with an eGFR <45 ml/min/1.73m^2 found no difference in treatment effect or adverse events compared to those with an eGFR >45 ml/min/1.73m^2.[71] These analyses, however, were limited by small sample sizes and included few patients with advanced CKD (the trial of risedronate had 75 patients with an eGFR of 13-23 ml/min/1.73m^2 while the trial of alendronate did not have any patients with an eGFR <15 ml/min/1.73m^2).[70,71] Evidence on the efficacy of bisphosphonates in patients with advanced kidney disease and in those receiving dialysis is limited to studies of safety or to case series, and show that there may be some mitigation of bone loss with bisphosphonates but no clear increase in BMD.[69,72,73]

Denosumab

Denosumab is an alternative anti-resorptive agent that is not cleared by the kidneys, making it an appealing option for individuals with advanced CKD.[74] Post hoc analyses of large efficacy trials of denosumab in the general population found no difference in fracture prevention or adverse events compared to placebo in those with mild or moderate CKD and those without.[75,76] However, studies included small numbers of individuals with an eGFR <30ml/min/1.73m^2 (63 in the original study and 9 in a longer term follow up). [75,76]

Studies of denosumab in patients receiving dialysis have typically been limited to the assessment of bone mineral density and there are no studies assessing fracture prevention. Three uncontrolled studies showed an increase in BMD at the femoral neck and lumbar spine over time among patients receiving dialysis, one of which also included patients with CKD not receiving dialysis.[77–79] However, there have been several case reports of severe hypocalcemia associated with denosumab use particularly in those with CKD.[78–81] The exact incidence and risk factors for this are not yet well described.

Anabolic Therapy

Anabolic therapies include medications that focus specifically on building bone. Two commonly used medications in this category are teriparatide and romosozumab, both of which have very limited evidence in CKD. Teriparatide, which is an analog of parathyroid hormone, is renally cleared, complicating its use in individuals with CKD. A post hoc analysis of a post-marketing observational trial showed that teriparatide may be successful in increasing bone density in individuals with an eGFR <30 ml/min/1.73m^2; however, less than 40 people with this level of kidney function were included.[82] In patients receiving dialysis, there are three small cohorts showing an increase in BMD at the lumbar spine, but no assessment of fracture outcomes.[83–85]

Romosozumab is a monoclonal antibody that inhibits sclerostin and prevents fractures in the general population.[86] A single-dose pharmacokinetic study in patients with an eGFR <30 ml/min/1.73m^3 showed an increase in the maximum serum romosozumab concentration compared to the general population with no significant adverse events.[87] A post hoc analysis including individuals with an eGFR of 30-59 ml/min/1.73m^2 showed a

similar efficacy in terms of fracture reduction compared to those with normal kidney function.[88] One case report and one small observational cohort of 76 of patients receiving dialysis showed an increase in bone density, but did not examine fracture risk.[89,90]

1.6 The need for research on fragility fracture prevention in CKD and dialysis

Despite the impact of fragility fractures in patients with CKD, few high-quality research studies have been conducted in this patient population. Most studies of risk factors for fracture in individuals receiving dialysis have been limited by small sample sizes and cross-sectional designs. Some medications commonly prescribed to individuals with CKD may increase their risk of fracture, and one large trial of SGLT-2i showed an increased risk of fracture patients in the general population who received canagliflozin vs placebo.[62] One of the proposed mechanisms of this increased risk is the potentiation of bone turnover and increased parathyroid levels, which is a process similar to that seen in advanced CKD.[66] However, there have not been any studies that have specifically examined the interaction between CKD and SGLT-2 inhibitors. Given that SGLT-2 inhibitors are now recommended as second line in diabetes guidelines, it is increasingly important to understand how SGLT-2 inhibitors may alter fracture risk in CKD. [91]

The current literature also focusses primarily on fracture risk scores used in the general population (FRAX and BMD), and do not consider the unique differences in bone physiology in patients with advanced kidney disease.[38] There is a great need for a simple, pragmatic method of estimating fracture risk in individuals receiving dialysis so that they can be targeted for therapy or included in clinical trials.

Moreover, once individuals with CKD have been identified as high risk of fracture, the treatment options are limited. Denosumab is a promising medication; however, there have been severe cases of hypocalcemia reported with its use.[74,78,79,81] Randomized controlled trials of its efficacy were limited in assessing this as they did not routinely draw calcium values after administration of the medication, and included relatively healthier patients (i.e., younger individuals with a lower degree of CKD) compared to real-world users.[92–94]

Before denosumab is widely adopted for fracture prevention, it is crucial that the degree of, and risks for, severe hypocalcemia are better described.

1.7 Research Objectives:

This thesis has three primary research objectives:

1. Develop a risk score using easily obtainable demographic and biochemical information to predict the 1 and 3-year risk of fracture in patients receiving dialysis.
2. Determine the risk of fracture in patients over 65 newly prescribed SGLT-2 inhibitors versus dipeptidyl peptidase IV inhibitors across all stages of chronic kidney disease in patients over 65.
3. Determine the incidence of and risk factors for hypocalcemia in patients over 65 who were newly prescribed denosumab compared to bisphosphonates across the spectrum chronic kidney disease.

Chapter 2 will explore the literature on risk scores currently used to predict fractures in patients receiving dialysis and chapter 3 will detail the creation of a new dialysis-specific risk score. Chapter 4 will explore SGLT-2i as another potential risk factor for fracture in patients with CKD and chapter 5 will examine the incidence and risk factors for hypocalcemia with denosumab, a promising treatment for reducing fracture risk. Chapter 6 will conclude with a discussion of the three articles as well as their shared strengths and limitations.

1.8 References

1. Mitchell PJ, Chan DC (Derrick), Lee JK, Tabu I, Alpuerto BB. The global burden of fragility fractures – what are the differences, and where are the gaps. *Best Pract Res Clin Rheumatol*. 2022;36(3). doi:10.1016/j.berh.2022.101777

2. Hopkins RB, Burke N, Von Keyserlingk C, et al. The current economic burden of illness of osteoporosis in Canada. *Osteoporosis International*. 2016;27(10):3023-3032. doi:10.1007/s00198-016-3631-6

3. Lubwama R, Nguyen A, Modi A, Diana C, Miller PD. Prevalence of renal impairment among osteoporotic women in the USA, NHANES 2005-2008: Is treatment with bisphosphonates an option? *Osteoporosis International*. 2014;25(5):1607-1615. doi:10.1007/s00198-014-2645-1

4. Naylor KL, McArthur E, Leslie WD, et al. The three-year incidence of fracture in chronic kidney disease. *Kidney Int*. 2014;86(4):810-818. doi:10.1038/ki.2013.547

5. Alem AM, Sherrard DJ, Gillen DL, et al. Increased risk of hip fracture among patients with end-stage renal disease. *Kidney Int*. 2000;58(1):396-399. doi:10.1046/j.1523-1755.2000.00178.x

6. Goto NA, Weststrate ACG, Oosterlaan FM, et al. The association between chronic kidney disease, falls, and fractures: a systematic review and meta-analysis. *Osteoporosis International*. 2020;31(1):13-29. doi:10.1007/s00198-019-05190-5

7. Kettler M, Leonard MB, on behalf of the Work Group. KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD). Published 2017. Accessed October 7, 2022. https://kdigo.org/guidelines/ckd-mbd/

8. Cozzolino M, Ureña-Torres P, Vervloet MG, et al. Is chronic kidney disease-mineral bone disorder (CKD-MBD) really a syndrome? *Nephrology Dialysis Transplantation*. 2014;29(10):1815-1820. doi:10.1093/ndt/gft514

9. Liu P, Quinn RR, Lam NN, et al. Progression and Regression of Chronic Kidney Disease by Age among Adults in a Population-Based Cohort in Alberta, Canada. *JAMA Netw Open*. Published online 2021. doi:10.1001/jamanetworkopen.2021.12828

10. Canadian Institute for Health Information. Treatment of End-Stage Organ Failure in Canada, Canadian Organ Replacement Register, 2011 to 2020: End-Stage Kidney Disease and Kidney Transplants — Data Tables. CIHI. Published 2021. Accessed July 10, 2022. https://www.cihi.ca/en/organ-replacement-in-canada-corr-annual-statistics

11. Public Health Agency of Canada. *Osteoporosis and Related Fractures in Canada : Report from the Canadian Chronic Disease Surveillance System.*; 2020.

12. Vestergaard P. Discrepancies in bone mineral density and fracture risk in patients with type 1 and type 2 diabetes - A meta-analysis. *Osteoporosis International*. 2007;18(4):427-444. doi:10.1007/s00198-006-0253-4

13. Schwartz A v, Hillier TA, Sellmeyer DE, et al. Older Women With Diabetes Have a Higher Risk of Falls A prospective study. *Diabetes Care*. 2002;25:1749-1754.

14. Arora P, Vasa P, Brenner D, et al. Prevalence estimates of chronic kidney disease in Canada: Results of a nationally representative survey. *CMAJ Canadian Medical Association Journal*. 2013;185(9). doi:10.1503/cmaj.120833

15. Ensrud KE, Ewing SK, Taylor BC, et al. Frailty and Risk of Falls, Fracture, and Mortality in Older Women: The Study of Osteoporotic Fractures. *Journal of Gerentology*. 2007;62A(7):744-751. https://academic.oup.com/biomedgerontology/article/62/7/744/581910

16. Wu PY, Chao C ter, Chan DC, Huang JW, Hung KY. Contributors, risk associates, and complications of frailty in patients with chronic kidney disease: a scoping review. *Ther Adv Chronic Dis*. 2019;10. doi:10.1177/2040622319880382

17. Coco M, Rush H. Increased incidence of hip fractures in dialysis patients with low serum parathyroid hormone. *American Journal of Kidney Diseases*. 2000;36(6):1115-1121. doi:10.1053/ajkd.2000.19812

18. Wakasugi M, Kazama JJ, Taniguchi M, et al. Increased risk of hip fracture among Japanese hemodialysis patients. *J Bone Miner Metab*. 2013;31(3):315-321. doi:10.1007/s00774-012-0411-z

19. Maravic M, Ostertag A, Torres PU, Cohen-Solal M. Incidence and risk factors for hip fractures in dialysis patients. *Osteoporosis International*. 2014;25(1):159-165. doi:10.1007/s00198-013-2435-1

20. Iseri K, Carrero JJ, Evans M, et al. Major fractures after initiation of dialysis: Incidence, predictors and association with mortality. *Bone*. 2020;133. doi:10.1016/j.bone.2020.115242

21. Jadoul M, Albert JM, Akiba T, et al. Incidence and risk factors for hip or other bone fractures among hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study. *Kidney Int*. 2006;70(7):1358-1366. doi:10.1038/sj.ki.5001754

22. Hsiue PP, Seo LJ, Sanaiha Y, Chen CJ, Khoshbin A, Stavrakis AI. Effect of Kidney Disease on Hemiarthroplasty Outcomes after Femoral Neck Fractures. *J Orthop Trauma*. 2019;33(11):583-589. doi:10.1097/BOT.0000000000001576

23. Ongzalima C, Dasborough K, Narula S, Boardman G, Kumarasinghe P, Seymour H. Perioperative Management and Outcomes of Hip Fracture Patients with Advanced Chronic Kidney Disease. *Geriatr Orthop Surg Rehabil*. 2022;13. doi:10.1177/21514593221138658

24. Huang PH, Chen TH, Lin YS, et al. Chronic Kidney Disease Worsens Health Outcomes in Diabetic Patients After Hip Fracture Surgery: An Asian Nationwide Population-Based Cohort Study. *Journal of Bone and Mineral Research*. 2019;34(5):849-858. doi:10.1002/jbmr.3663

25. Chen CT, Lin SJ, Kuo LT, et al. Effect of chronic kidney disease on outcomes following proximal humerus fragility fracture surgery in diabetic patients: A nationwide population-based cohort study. *PLoS One*. 2021;16(10 October). doi:10.1371/journal.pone.0258393

26. Nitsch D, Mylne A, Roderick PJ, Smeeth L, Hubbard R, Fletcher A. Chronic kidney disease and hip fracture-related mortality in older people in the UK. *Nephrology Dialysis Transplantation*. 2009;24(5):1539-1544. doi:10.1093/ndt/gfn678

27. Robertson L, Black C, Fluck N, et al. Hip fracture incidence and mortality in chronic kidney disease: The GLOMMS-II record linkage cohort study. *BMJ Open*. 2018;8(4). doi:10.1136/bmjopen-2017-020312

28. Nair SS, Mitani AA, Goldstein BA, Chertow GM, Lowenberg DW, Winkelmayer WC. Temporal trends in the incidence, treatment, and outcomes of hip fracture in older patients initiating dialysis in the United States. *Clinical Journal of the American Society of Nephrology*. 2013;8(8):1336-1342. doi:10.2215/CJN.10901012

29. Lo LWT, Yanling X, Chou ACC, Howe T Sen, Allen JC, Koh JSB. End-stage renal failure is an independent risk factor for 1-year mortality after hip fracture surgery. *Geriatr Orthop Surg Rehabil*. 2018;9. doi:10.1177/2151459318770561

30. Downey C, Kelly M, Quinlan JF. Changing trends in the mortality rate at 1-year post hip fracture - a systematic review. *World J Orthop*. 2019;10(3):166-175. doi:10.5312/wjo.v10.i3.166

31. Mittalhenkle A, Gillen DL, Stehman-Breen CO. Increased risk of mortality associated with hip fracture in the dialysis population. *American Journal of Kidney Diseases*. 2004;44(4):672-679. doi:10.1053/j.ajkd.2004.07.001

32. Beaubrun AC, Kilpatrick RD, Freburger JK, Bradbury BD, Wang L, Brookhart MA. Temporal trends in fracture rates and postdischarge outcomes among hemodialysis patients. *Journal of the American Society of Nephrology*. 2013;24(9):1461-1469. doi:10.1681/ASN.2012090916

33. Yenchek RH, Ix JH, Shlipak MG, et al. Bone Mineral Density and Fracture Risk in Older Individuals with CKD. *Clin J Am Soc Nephrol*. 2012;7(July 1998):1130-1136. doi:10.2215/CJN.12871211

34. Prasad B, Ferguson T, Tangri N, Ng CY, Nickolas TL. Association of Bone Mineral Density With Fractures Across the Spectrum of Chronic Kidney Disease : The Regina CKD-MBD Study. *Can J Kidney Health Dis*. 2019;6:1-10. doi:10.1177/2054358119870539

35. Nickolas TL, Stein E, Cohen A, et al. Bone mass and microarchitecture in CKD patients with fracture. *Journal of the American Society of Nephrology*. 2010;21(8):1371-1380. doi:10.1681/ASN.2009121208

36. Nickolas TL, Cremers S, Zhang A, et al. Discriminants of prevalent fractures in chronic kidney disease. *Journal of the American Society of Nephrology*. 2011;22(8):1560-1572. doi:10.1681/ASN.2010121275

37. Bucur RC, Panjwani DD, Turner L, Rader T, West SL, Jamal SA. Low bone mineral density and fractures in stages 3–5 CKD: an updated systematic review and meta-analysis. *Osteoporosis International*. 2015;26(2):449-458. doi:10.1007/s00198-014-2813-3

38. Leslie WD, Lix LM, Langsetmo L, et al. Construction of a FRAX® model for the assessment of fracture probability in Canada and implications for treatment. *Osteoporosis International*. 2011;22(3):817-827. doi:10.1007/s00198-010-1464-2

39. Young TK, Toussaint ND, Di Tanna GL, et al. Risk Factors for Fracture in Patients with Coexisting Chronic Kidney Disease and Type 2 Diabetes: An Observational Analysis from the CREDENCE Trial. *J Diabetes Res*. 2022;2022. doi:10.1155/2022/9998891

40. Kim SH, Yi SW, Yi JJ, Kim YM, Won YJ. Chronic Kidney Disease Increases the Risk of Hip Fracture: A Prospective Cohort Study in Korean Adults. *Journal of Bone and Mineral Research*. 2020;35(7):1313-1321. doi:10.1002/jbmr.3997

41. Kaneko TM, Foley RN, Gilbertson DT, Collins AJ. Clinical epidemiology of long-bone fractures in patients receiving hemodialysis. *Clin Orthop Relat Res*. 2007;457:188-193. doi:10.1097/BLO.0b013e318031465b

42. Stehman-Breen CO, Sherrard DJ, Alem AM, et al. Risk factors for hip fracture among patients with end-stage renal disease. *Kidney Int*. 2000;58(5):2200-2205. doi:10.1111/j.1523-1755.2000.00394.x

43. Inaba M, Okuno S, Kumeda Y, Yamakawa T, Ishimura E, Nishizawa Y. Increased incidence of vertebral fracture in older female hemodialyzed patients with type 2 diabetes mellitus. *Calcif Tissue Int*. 2005;76(4):256-260. doi:10.1007/s00223-004-0094-0

44. Ball AM, Gillen DL, Sherrard D, et al. *Risk of Hip Fracture Among Dialysis and Renal Transplant Recipients*.; 2002. https://jamanetwork.com/

45. Danese MD, Kim J, Doan Q v., Dylan M, Griffiths R, Chertow GM. PTH and the risks for hip, vertebral, and pelvic fractures among patients on dialysis. *American Journal of Kidney Diseases*. 2006;47(1):149-156. doi:10.1053/j.ajkd.2005.09.024

46. Ureña P, Bernard-Poenaru O, Ostertag A, et al. Bone mineral density, biochemical markers and skeletal fractures in haemodialysis patients. *Nephrology Dialysis Transplantation*. 2003;18(11):2325-2331. doi:10.1093/ndt/gfg403

47. Kaji H, Suzuki M, Yano S, et al. *Risk Factors for Hip Fracture in Hemodialysis Patients*. Vol 22.; 2002. www.karger.com

48. Iimori S, Mori Y, Akita W, et al. Diagnostic usefulness of bone mineral density and biochemical markers of bone turnover in predicting fracture in CKD stage 5D patients-a single-center cohort study. *Nephrology Dialysis Transplantation*. 2012;27(1):345-351. doi:10.1093/ndt/gfr317

49. Brunerová L, Lažanská R, Kasalický P, et al. Predictors of bone fractures in a single-centre cohort of hemodialysis patients: a 2-year follow-up study. *Int Urol Nephrol*. 2018;50(9):1721-1728. doi:10.1007/s11255-018-1958-y

50. Papaioannou A, Morin S, Cheung AM, et al. 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: Summary. *CMAJ*. 2010;182(17):1864-1873. doi:10.1503/cmaj.100771

51. Jamal SA, Hayden JA, Beyene J. Low Bone Mineral Density and Fractures in Long-Term Hemodialysis Patients: A Meta-Analysis. *American Journal of Kidney Diseases*. 2007;49(5):674-681. doi:10.1053/j.ajkd.2007.02.264

52. Chang A j., Ying Q, Chen X n., Wang W m., Chen N. Evaluation of three risk assessment tools in discriminating fracture status among Chinese patients undergoing hemodialysis. *Osteoporosis International*. 2016;27(12):3599-3606. doi:10.1007/s00198-016-3690-8

53. Poiana C, Dusceac R, Niculescu DA. Utility of Trabecular Bone Score (TBS) in Bone Quality and Fracture Risk Assessment in Patients on Maintenance Dialysis. *Front Med (Lausanne)*. 2022;8. doi:10.3389/fmed.2021.782837

54. Rampersad C, Whitlock RH, Leslie WD, et al. Trabecular bone score in patients with chronic kidney disease. *Osteoporosis International*. 2020;31(10):1905-1912. doi:10.1007/s00198-020-05458-1

55. Kanis JA, Johansson H, Oden A, et al. A meta-analysis of prior corticosteroid use and fracture risk. *Journal of Bone and Mineral Research*. 2004;19(6):893-899. doi:10.1359/JBMR.040134

56. Devraj R, Deshpande M. Demographic and health-related predictors of proton pump inhibitor (PPI) use and association with chronic kidney disease (CKD) stage in NHANES population. In: *Research in Social and Administrative Pharmacy*. Vol 16. Elsevier Inc.; 2020:776-782. doi:10.1016/j.sapharm.2019.08.032

57. Lee HJ, Lee H, Oh SH, et al. Chronic kidney disease (CKD) patients are exposed to more proton pump inhibitor (PPI)s compared to non-CKD patients. *PLoS One*. 2018;13(9). doi:10.1371/journal.pone.0203878

58. Thong BKS, Ima-Nirwana S, Chin KY. Proton pump inhibitors and fracture risk: A review of current evidence and mechanisms involved. *Int J Environ Res Public Health*. 2019;16(9). doi:10.3390/ijerph16091571

59. Nassar Y, Richter S. Proton-pump Inhibitor Use and Fracture Risk: An Updated Systematic Review and Meta-analysis. *J Bone Metab*. 2018;25(3):141. doi:10.11005/jbm.2018.25.3.141

60. Hussain S, Siddiqui AN, Habib A, Hussain MS, Najmi AK. Proton pump inhibitors' use and risk of hip fracture: a systematic review and meta-analysis. *Rheumatol Int*. 2018;38(11):1999-2014. doi:10.1007/s00296-018-4142-x

61. Fusaro M, D'Arrigo G, Pitino A, et al. Increased Risk of Bone Fractures in Hemodialysis Patients Treated with Proton Pump Inhibitors in Real World: Results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Journal of Bone and Mineral Research*. 2019;34(12):2238-2245. doi:10.1002/jbmr.3842

62. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *New England Journal of Medicine*. 2017;377(7):644-657. doi:10.1056/NEJMoa1611925

63. Watts NB, Bilezikian JP, Usiskin K, et al. Effects of canagliflozin on fracture risk in patients with type 2 diabetes mellitus. *Journal of Clinical Endocrinology and Metabolism*. 2016;101(1):157-166. doi:10.1210/jc.2015-3167

64. Kohan DE, Fioretto P, Tang W, List JF. Long-term study of patients with type 2 diabetes and moderate renal impairment shows that dapagliflozin reduces weight and blood pressure but does not improve glycemic control. *Kidney Int*. 2014;85(4):962-971. doi:10.1038/ki.2013.356

65. Bilezikian JP, Watts NB, Usiskin K, et al. Evaluation of bone mineral density and bone biomarkers in patients with type 2 diabetes treated with canagliflozin. *Journal of Clinical Endocrinology and Metabolism*. 2016;101(1):44-51. doi:10.1210/jc.2015-1860

66. Weir MR, Kline I, Xie J, Edwards R, Usiskin K. Effect of canagliflozin on serum electrolytes in patients with type 2 diabetes in relation to estimated glomerular filtration rate (eGFR). *Curr Med Res Opin*. 2014;30(9):1759-1768. doi:10.1185/03007995.2014.919907

67. Torregrosa J V., Ramos AM. Use of Bisphosphonates in Chronic Kidney Disease. *Nefrologia*. 2010;30(3):288-297. doi:10.3265/Nefrologia.pre2010.Mar.10320

68. Iseri K, Watanabe M, Yoshikawa H, et al. Effects of Denosumab and Alendronate on Bone Health and Vascular Function in Hemodialysis Patients: A Randomized, Controlled Trial. *Journal of Bone and Mineral Research*. 2019;34(6):1014-1024. doi:10.1002/jbmr.3676

69. Wetmore JB, Benet LZ, Kleinstuck D, Frassetto L. Effects of short-term alendronate on bone mineral density in haemodialysis patients. *Nephrology*. 2005;10(4):393-399. doi:10.1111/j.1440-1797.2005.00436.x

70. Miller PD, Roux C, Boonen S, Barton IP, Dunlap LE, Burgio DE. Safety and efficacy of risedronate in patients with age-related reduced renal function as estimated by the Cockcroft and Gault method: A pooled analysis of nine clinical trials. *Journal of Bone and Mineral Research*. 2005;20(12):2105-2115. doi:10.1359/JBMR.050817

71. Jamal SA, Bauer DC, Ensrud KE, et al. Alendronate treatment in women with normal to severely impaired renal function: An analysis of the fracture intervention trial. *Journal of Bone and Mineral Research*. 2007;22(4):503-508. doi:10.1359/jbmr.070112

72. Robinson DE, Ali MS, Pallares N, et al. Safety of Oral Bisphosphonates in Moderate-to-Severe Chronic Kidney Disease: A Binational Cohort Analysis. *Journal of Bone and Mineral Research*. 2021;36(5):820-832. doi:10.1002/jbmr.4235

73. Hauck D, Nery L, O'Connell R, Clifton-Bligh R, Mather A, Girgis CM. Bisphosphonates and bone mineral density in patients with end-stage kidney disease and renal transplants: A 15-year single-centre experience. *Bone Rep*. 2022;16. doi:10.1016/j.bonr.2022.101178

74. Block GA, Bone HG, Fang L, Lee E, Padhi D. A single-dose study of denosumab in patients with various degrees of renal impairment. *Journal of Bone and Mineral Research*. 2012;27(7):1471-1479. doi:10.1002/jbmr.1613

75. Jamal SA, Ljunggren Ö, Stehman-Breen C, et al. Effects of denosumab on fracture and bone mineral density by level of kidney function. *Journal of Bone and Mineral Research*. 2011;26(8):1829-1835. doi:10.1002/jbmr.403

76. Broadwell A, Chines A, Ebeling PR, et al. Denosumab Safety and Efficacy Among Participants in the FREEDOM Extension Study With Mild to Moderate Chronic Kidney Disease. *J Clin Endocrinol Metab*. 2021;106(2):397-409. doi:10.1210/clinem/dgaa851

77. Chen CL, Chen NC, Hsu CY, et al. An Open-Label, Prospective Pilot Clinical Study of Denosumab for Severe Hyperparathyroidism in Patients With Low Bone Mass Undergoing Dialysis. *J Clin Endocrinol Metab*. 2014;99(7):2426-2432. doi:10.1210/jc.2014-1154

78. Hiramatsu R, Ubara Y, Sawa N, Sakai A. Hypocalcemia and bone mineral changes in hemodialysis patients with low bone mass treated with denosumab: a 2-year observational study. *Nephrology Dialysis Transplantation*. 2021;36(10):1900-1907. doi:10.1093/ndt/gfaa359

79. Kunizawa K, Hiramatsu R, Hoshino J, et al. Denosumab for dialysis patients with osteoporosis: A cohort study. *Sci Rep*. 2020;10(1):2496. doi:10.1038/s41598-020-59143-8

80. Block G, Egbuna O, Zeig S, et al. The evaluation of denosumab safety in patients with chronic kidney disease: An open-label study. *Journal of Clinical Oncology*. 2014;32(15_suppl):e20649-e20649. doi:10.1200/jco.2014.32.15_suppl.e20649

81. Dave V, Chiang CY, Booth J, Mount PF. Hypocalcemia post denosumab in patients with chronic kidney disease stage 4-5. *Am J Nephrol*. 2015;41(2):129-137. doi:10.1159/000380960

82. Nishikawa A, Yoshiki F, Taketsuna M, Kajimoto K, Enomoto H. Safety and effectiveness of daily teriparatide for osteoporosis in patients with severe stages of chronic kidney disease: Post hoc analysis of a postmarketing observational study. *Clin Interv Aging*. 2016;11:1653-1659. doi:10.2147/CIA.S120175

83. Sumida K, Ubara Y, Hoshino J, et al. Once-weekly teriparatide in hemodialysis patients with hypoparathyroidism and low bone mass: a prospective study. *Osteoporosis International*. 2016;27(4):1441-1450. doi:10.1007/s00198-015-3377-6

84. Yamamoto J, Nakazawa D, Nishio S, et al. Impact of Weekly Teriparatide on the Bone and Mineral Metabolism in Hemodialysis Patients With Relatively Low Serum Parathyroid Hormone: A Pilot Study. *Therapeutic Apheresis and Dialysis*. 2020;24(2):146-153. doi:10.1111/1744-9987.12867

85. Cejka D, Kodras K, Bader T, Haas M. Treatment of hemodialysis-associated adynamic bone disease with teriparatide (PTH1-34): A pilot study. *Kidney Blood Press Res*. 2010;33(3):221-226. doi:10.1159/000316708

86. Cosman F, Crittenden DB, Ferrari S, et al. FRAME Study: The Foundation Effect of Building Bone With 1 Year of Romosozumab Leads to Continued Lower Fracture Risk After Transition to Denosumab. *Journal of Bone and Mineral Research*. 2018;33(7):1219-1226. doi:10.1002/jbmr.3427

87. Hsu CP, Maddox J, Block G, Bartley Y, Yu Z. Influence of Renal Function on Pharmacokinetics, Pharmacodynamics, and Safety of a Single Dose of Romosozumab. *J Clin Pharmacol*. 2022;62(9):1132-1141. doi:10.1002/jcph.2050

88. Miller PD, Adachi JD, Albergaria BH, et al. Efficacy and Safety of Romosozumab Among Postmenopausal Women With Osteoporosis and Mild-to-Moderate Chronic Kidney Disease. *Journal of Bone and Mineral Research*. 2022;37(8):1437-1445. doi:10.1002/jbmr.4563

89. Sato M, Inaba M, Yamada S, Emoto M, Ohno Y, Tsujimoto Y. Efficacy of romosozumab in patients with osteoporosis on maintenance hemodialysis in Japan; an observational study. *J Bone Miner Metab*. 2021;39(6):1082-1090. doi:10.1007/s00774-021-01253-y

90. Suzuki T, Mizobuchi M, Yoshida S, et al. Romosozumab successfully regulated progressive osteoporosis in a patient with autosomal dominant polycystic kidney disease

undergoing hemodialysis. *Osteoporosis International*. 2022;33(12):2649-2652. doi:10.1007/s00198-022-06534-4

91. KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. *Kidney Int*. 2020;98(4):S1-S115. doi:10.1016/j.kint.2020.06.019

92. Clemens KK, Jeyakumar N, Alexandra OM, Jenny T, Tayyab K. Bisphosphonate and denosumab initiation in older adults in Ontario , Canada : a population-based cohort study. *Arch Osteoporos*. 2020;133(15).

93. Langdahl BL, Teglbjærg CS, Ho PR, et al. A 24-Month Study Evaluating the Efficacy and Safety of Denosumab for the Treatment of Men With Low Bone Mineral Density: Results From the ADAMO Trial. *J Clin Endocrinol Metab*. 2015;100(4):1335-1342. doi:10.1210/jc.2014-4079

94. Cummings SR, Martin JS, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *Obstet Gynecol Surv*. 2009;64(12):805-807. doi:10.1097/01.ogx.0000363236.41902.96

Chapter 2

2 Literature Review: Facture Prediction in Patients Receiving Dialysis

2. 1 Search Strategy and Quality Assessment

We conducted a literature review to identify prior studies that explored methods of predicting fracture risk in individuals receiving dialysis. MEDLINE and EMBASE databases were searched using the search strategy detailed in Appendix A. We also searched the reference lists of relevant articles, and by using the cited-by search function in Google Scholar.

Inclusion criteria were developed *a priori* and were as follows: i) full-text English language articles, ii) included patients receiving dialysis or reported a subgroup of patients receiving dialysis, iii) reported fracture as an outcome, and iv) reported model performance for fracture prediction (area under receiver operating curve [AUC], c-statistic and/or sensitivity/specificity). Studies were excluded they were i) editorials, narrative reviews, or commentaries and ii) explored individual risk factors for fracture but did not include a statistical prediction model.

We then assessed the quality of included articles using the Newcastle Ottawa Scale, using a modified version for cross-sectional studies.[1–3] The Newcastle Ottawa Scale rates studies on three areas: selection of the cases and controls and their representativeness (maximum 4 points for cohort studies and 5 points for cross-sectional studies), comparability of cases and controls (maximum 2 points), and ascertainment of the exposure (maximum 3 points).

Table 2.1 The Characteristics and Results of Studies Testing Risk Scores to Predict the Risk of Fracture

Author	Study Description	Results	Study Limitations	Newcastle Ottawa Score		
				Selection	Comparability	Outcome
Cohort Studies						
Przedlacki et al, 2018	- Prospective multicentre cohort study of 1,038 patients receiving hemodialysis in Poland - Calculated FRAX score without BMD - Followed individuals for two years or until first fracture	- 320 patients lost to follow up - 30/718 4.2% patients suffered a fracture over 2 years - AUC for FRAX result for major fracture was 0.76 - AUC for FRAX for hip fracture was 0.70	- Almost one third of patients were lost to follow up and not included in analysis - Small number of fractures observed	3	2	1
Przedlacki et al, 2020	- Extension of Prezedlacki et al , 2018 cohort (718 patients receiving hemodialysis in Poland). - Examined the ideal FRAX score cut-off for prediction of 2 year fracture risk	- A FRAX cut-off of >5% had a sensitivity of 70% and specificity of 70% for prediction of major osteoporotic fracture - This was better than previous fracture (sens 30% and spec 87%), and	- Almost one third of patients were lost to follow up and not included in analysis - Small number of fractures observed	3	2	1

	- Also examined the sensitivity and specificity of other risk factors in fracture prediction	previous glucocorticoids use, as defined in the FRAX score (sens 33% spec 89%), or PTH outside the range specified by KDIGO (sens 33%, specificity 89%)				
Iimori et al, 2012	- Cohort study of 485 patients receiving hemodialysis in Japan, followed for 5 years - Compared the diagnostic accuracy of BMD, bsALP and PTH	- 46/485 (9.5%) patients had a fracture over 3.3 years - AUC for BMD ranged from 0.56-0.59 depending on site - AUC for bsALP was 0.76 - AUC for PTH was 0.634	- Single centre cohort - bsALP values used were those closest to the fracture, not the baseline value - No description of the method of non-vertebral fracture ascertainment	4	2	1
Yamaguchi et al, 1996	- Followed a cohort of 124 patients receiving hemodialysis in Japan - Screened for asymptomatic vertebral fracture using spine x-ray	- For the prediction of non spine fracture, ultradistal radial BMD had the best prediction ability with an AUC of 0.86 - This was significantly better than the lumbar spine BMD	- Small sample size - Although it was a longitudinal cohort study, the inclusion of vertebral fracture detected by x-ray means some of the spinal fractures may have occurred prior to the study	4	2	2
Cross Sectional Studies						

Chang et al, 2016	- Cross sectional study of 136 patients receiving hemodialysis in China - Compared FRAX, BMD and OSTA in their ability to predict prevalent fracture	- Prevalence of fracture was 12% - Total hip BMD had the highest AUC (0.736) compared to BMD at other sites, FRAX (with and without BMD) and the OSTA but differences between AUC were not statistically significant	- Cross sectional - Differences in fracture rates by ethnicity limit the application of these results to predominantly Caucasian populations	1	2	2
Jafari et al, 2021	- Cross sectional study of 131 patients receiving hemodialysis in Saskatchewan, Canada - Compared BMD to FRAX with or without frailty and falls for prediction of fracture	- 22 participants excluded from follow-up - Prevalence of fracture was 37.6% - The addition of FRAX clinical variables increased the AUC compared to just BMD (AUC 0.78 vs 0.67) - The addition of frailty or a history of falls did not improve the AUC	- Small sample size - Cross sectional design	3	2	3
Jirasirirak et al, 2022	- Cross sectional study of 80 patients in Thailand - Assess the ability of FRAX	- Prevalence of asymptomatic vertebral fracture was 27.5% - The AUC for a clinical model containing	- Asymptomatic vertebral fractures are less relevant as the outcome	2	2	3

	(without BMD) to predict asymptomatic vertebral fractures compared to a model of clinical factors - Participants all had spine x-ray to determine the incidence of asymptomatic vertebral fracture	serum calcium, albumin and history of steroid use was 0.80 - AUC for FRAX alone was 0.64	- Cross sectional design - Small sample size			

AUC- area under the receiver operating curve; BMD- bone mineral density; sens- sensitivity; spec- specificity; bsALP- bone specific alkaline phosphatase; FRAX- fracture risk assessment tool; KDIGO- Kidney Disease Improving Global Outcomes OSTA- Osteoporosis Self Assessment Tool for Asians; PTH- parathyroid hormone; OSTA- Osteoporosis Self Assessment Tool for Asians; KDIGO- Kidney Disease Improving Global Outcomes

2.2 Summary of Existing Literature

Seven studies meeting the inclusion criteria were identified including four cohort studies and three cross sectional studies (see details in Table 1).[4–10] The most assessed risk score is the Fracture Risk Assessment Tool (FRAX) (https://frax.shef.ac.uk/). The variables included in FRAX are: age, sex, body mass index, previous fracture, parental hip fracture, history of smoking, glucocorticoid use (past or present exposure to more than 3 months of a steroid dose equivalent to ≥5mg of prednisone) rheumatoid arthritis, risk factors for secondary osteoporosis, >3 alcoholic drinks per day and the bone mineral density (BMD) at the femoral neck. In the general Canadian population, the FRAX score predicts major osteoporotic fracture modestly with an AUC of 0.69 while prediction of hip fracture is better with an AUC of 0.8. Five studies tested the predictive ability of FRAX in patients receiving dialysis. Three studies excluded the BMD variable, while two examined it both with and without the BMD variable. Depending on which FRAX score was used (risk of hip or major osteoporotic fracture) and whether BMD was included, the AUC for FRAX ranged from 0.70 to 0.78.[4–8]

Four studies examined the predictive power of BMD alone, with AUC ranging from 0.59-0.87.[6,7,9,10] There was no clear pattern of any anatomical site consistently performing better than another. Two studies compared FRAX and BMD. One study found that FRAX with BMD had higher discrimination compared to just BMD (AUC 0.67 for BMD alone and 0.78 for FRAX likelihood ratio test $p<0.001$).[7] Another study however, showed that total hip BMD performed numerically better than the FRAX score (AUC 0.74 vs 0.72) but there was no statistically significant difference found between the two. [6]

Three other studies examined other methods of risk prediction such as alternative calculators or biochemical indices.[6,8,9] One cohort study found that the AUC for bone-specific alkaline phosphatase alone was 0.76, which was superior to parathyroid hormone (AUC-0.63).[9] Another cross-sectional study examined the Osteoporosis Self-Assessment Tool for Asians which is a simple tool that uses age and body weight to determine risk. There was no significant difference in the performance of this tool compared to using BMD alone or FRAX with BMD.[6] Finally, a cross-sectional study showed that a model

combining calcium, albumin and a history of steroid use had an AUC of 0.8 for the prediction of asymptomatic vertebral fractures.[8]

2.3 Conclusion

The evidence around fracture risk prediction in patients receiving dialysis is limited. Studies of FRAX, the most commonly used score in patients receiving dialysis, have been limited by small sample sizes (<800 patients) and low event rates (<50 fractures) in longitudinal studies. Similarly, single-centre studies of FRAX, BMD or biochemical risk factors have limited generalizability as fracture rates vary considerably by ethnicity and geography.[11] Finally, cross-sectional designs, which were commonly used, do not allow for the prediction of incident fractures and have excluded individuals who die shortly after their fracture, biasing the group included to a less frail cohort. Ideally, a large, multi-jurisdictional, longitudinal study of potential fracture risk prediction tools are needed to develop a method of identifying patients receiving dialysis who are at high risk of fracture.

2.4 References

1. Modesti PA, Reboldi G, Cappuccio FP, et al. Panethnic differences in blood pressure in Europe: A systematic review and meta-analysis. *PLoS One*. 2016;11(1). doi:10.1371/journal.pone.0147601

2. Herzog R, Álvarez-Pasquin MJ, Díaz C, del Barrio JL, Estrada JM, Gil Á. Are healthcare workers intentions to vaccinate related to their knowledge, beliefs and attitudes? A systematic review. *BMC Public Health*. 2013;13(1). doi:10.1186/1471-2458-13-154

3. Dubey VP, Kievišienė J, Rauckiene-Michealsson A, Norkiene S, Razbadauskas A, Agostinis-Sobrinho C. Bullying and Health Related Quality of Life among Adolescents—A Systematic Review. *Children*. 2022;9(6):766. doi:10.3390/children9060766

4. Przedlacki J, Buczyńska-Chyl J, Koźmiński P, et al. The utility of FRAX® in predicting bone fractures in patients with chronic kidney disease on hemodialysis: a two-year prospective multicenter cohort study. *Osteoporosis International*. 2018;29(5):1105-1115. doi:10.1007/s00198-018-4406-z

5. Przedlacki J, Buczyńska-Chyl J, Koźmiński P, et al. FRAX prognostic and intervention thresholds in the management of major bone fractures in hemodialysis patients: A two-year prospective multicenter cohort study. *Bone*. 2020;133. doi:10.1016/j.bone.2019.115188

6. Chang A j., Ying Q, Chen X n., Wang W m., Chen N. Evaluation of three risk assessment tools in discriminating fracture status among Chinese patients undergoing hemodialysis. *Osteoporosis International*. 2016;27(12):3599-3606. doi:10.1007/s00198-016-3690-8

7. Jafari M, Anwar S, Kour K, Sanjoy S, Goyal K, Prasad B. T Scores, FRAX, Frailty Phenotype, Falls, and Its Relationship to Fractures in Patients on Maintenance Hemodialysis. *Can J Kidney Health Dis*. 2021;8:205435812110411. doi:10.1177/20543581211041184

8. Jirasirirak S, Disthabanchong S, Ongphiphadhanakul B, Arj-Ong Vallibhakara S, Nimitphong H. Prevalence and predictors of asymptomatic vertebral fracture in patients with end-stage renal disease. *Heliyon*. 2022;8(3). doi:10.1016/j.heliyon.2022.e09158

9. Iimori S, Mori Y, Akita W, et al. Diagnostic usefulness of bone mineral density and biochemical markers of bone turnover in predicting fracture in CKD stage 5D patients-a single-center cohort study. *Nephrology Dialysis Transplantation*. 2012;27(1):345-351. doi:10.1093/ndt/gfr317

10. Yamaguchi T, Kanno ' E, Tsubota J, Shiomi ' T, Nakai,' ' M, Hattori' S. *Retrospective Study on the Usefulness of Radius and Lumbar Bone Density in the Separation of Hemodialysis Patients with Fractures from Those Without Fractures*. Vol 19.; 1996.

11. Wu AM, Bisignano C, James SL, et al. Global, regional, and national burden of bone fractures in 204 countries and territories, 1990–2019: a systematic analysis from the Global Burden of Disease Study 2019. *Lancet Healthy Longev*. 2021;2(9):e580-e592. doi:10.1016/S2666-7568(21)00172-0

Chapter 3

3 Fracture Risk Prediction in Patients Receiving Dialysis

Cowan, Andrea C J[1,3], Kang, Yuguang[1], Dixon, Stephanie N.[1,2,4], Jeyakumar, Nivethika[1], Sontrop, Jessica[2], Clemens, Kristin K.[1,2,3,4,5], Garg, Amit X.[1,2,3,4]

1. ICES, ON, Canada
2. Department of Epidemiology & Biostatistics, Western University, London ON, Canada
3. Department of Medicine, Western University, London ON, Canada
4. Lawson Health Research Institute, London ON, Canada
5. St. Joseph's Health Care London, London ON, Canada

3.1 Introduction

Patients receiving maintenance dialysis are at a 5-fold increased risk of fracture compared to those with normal renal function.[1–3] Those who suffer a fracture have a 50% risk of mortality at 1-year, double that of the general population, and double that of their peers receiving dialysis without a fracture.[3–8]

Despite this, we have little evidence on how to identify those who are at highest risk of fragility fracture. Understanding fracture risk is extremely important in dialysis populations given current treatments to reduce fracture in patients with kidney disease can have significant side effects (e.g. hypocalcaemia with denosumab, or the risk of atypical femoral fractures with bisphosphonates, increased risk of cardiovascular disease with romosozumab) making it even more important to target those individuals truly at high potential.[9–11]

While fracture risk tools exist in the general population (i.e. bone mineral density [BMD] and the Fracture Risk Assessment Tool [FRAX]) and are well validated in the general population, their utility in patients receiving dialysis is less clear. When studied, the relationship between BMD and fracture risk in patients receiving dialysis has proven inconsistent, due to small study sizes and cross-sectional design of prior studies.[12–18]

BMD also fails to account for other changes unique to CKD-MBD that increase fracture risk. For example, hyperparathyroidism disproportionately decreases cortical bone density with relative preservation of trabecular bone, meaning its effects are not well detected when measuring bone density at the lumbar spine (which is comprised primarily of trabecular bone).[13,19] In light of a modest predictive power demonstrated in more recent studies, bone mineral density testing was recommended in the 2017 KDIGO chronic kidney disease- mineral bone disorder (CKD-MBD) guidelines if it would change the patient's management.[20]

Canadian osteoporosis guidelines recommend using the FRAX score to predict 10-year fracture risk in the general population.[21] However, this does not include kidney disease as a secondary risk factor for fracture, despite the increased risk seen in this population. In two cohorts of patients with chronic kidney disease, it was observed that FRAX predicted fracture risk equally well to the general population. However, these studies had small numbers of patients with advanced CKD included (210 with an eGFR <15 ml/min/1.73m^2 in one study and 13 patients with an eGFR <30 ml/min/1.73m^2 in another).[22,23] In patients receiving hemodialysis, FRAX performed reasonably for predicting fracture risk (area under receiver operating curve 0.70-0.78), but these studies were all small (sizes ranging from 80-485 patients) and three were cross-sectional.[17,24–27] Further, much like bone mineral density, the FRAX score does not address risk factors specific to patients receiving hemodialysis including CKD-MBD and hyperparathyroidism. FRAX can be cumbersome to calculate and requires an extra medical visit for bone mineral density testing.

Our objective was to create a tool to predict the 1-year and 3-year risk of fracture in patients receiving maintenance dialysis. We included clinically relevant, easily obtainable measures to make the tool easy to implement in both clinical and research settings.

3.2 Methods

3.2.1 Study design and setting

We conducted a population-based cohort study of adults in Ontario, Canada receiving chronic dialysis using linked administrative health data. All Ontario residents (~14 million) have universal access to insured hospital and physician services including dialysis, if indicated. The Ontario Drug Benefit (ODB) provides prescription drug coverage for anyone over 65 years of age or receiving social assistance programs. The use of data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act and the Research Ethics Board did not require additional review for the secondary use of administrative data. In this study we followed the TRIPOD guidelines for studies using healthcare databases (Transparent Reporting of a multIvariable Prediction mODel for individual prognosis or diagnosis; see appendix A.A).

3.2.2 Data Sources

Patient characteristics, baseline and outcome data were obtained from 11 health databases at ICES (ices.on.ca). ICES is an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement. Detailed information on these databases and variables can be found in Appendix A.B and A.C respectively. These datasets include the Canadian Institute for Health Information's Discharge Abstract Database [CIHI-DAD] and National Ambulatory Care Reporting System (CIHI-NACRS). Administrative codes (e.g. International Classification of Diseases 10th Revision) are entered into CIHI-DAD and CIHI-NACRS by trained medical coders. These personnel only assign codes based on diagnoses recorded by physicians. Prescribed medications were identified using the Ontario Drug Benefit Database (ODB). Of note, use of calcium carbonate, vitamin D3 or cinacalcet are not available through ODB.

Laboratory information was obtained from the Ontario Lab Information System (OLIS). For the study period, the most commonly used community laboratories in Ontario

contributed all laboratory data to OLIS, but hospital laboratory contributions (for both individuals admitted to hospital and outpatients who had their lab tests drawn at the hospital) were smaller. In 2017, 61.4% of Ontario's population lived in the catchment area of a hospital laboratory that contributed to OLIS.[28] [28] Only patients with a recorded parathyroid hormone (PTH) level were included (which, per guidelines is routinely drawn every 3-4 months in patients receiving dialysis).[29] As a result, both incident and prevalent dialysis patients were accrued as laboratory availability increased.

3.2.3 Population

We created a cohort of patients over 18 years of age receiving maintenance hemodialysis or peritoneal dialysis between January 1, 2010 and September 30, 2017. The index date was the date of the first available PTH measurement for an individual who had been receiving dialysis for at least 90 days prior. Patients were only enrolled after receiving dialysis for 90 days to ensure we were including stable recipients on maintenance dialysis and to exclude patients with an acute kidney injury who quickly recovered.

After data cleaning, we excluded the following patients: those aged <40 or >90 on the index date (to improve specificity for fragility fracture rather than traumatic fractures); those who had a prescription for bisphosphonates, denosumab or raloxifene in the 365 days prior to index date, as these are uncommonly prescribed in the dialysis population and can alter fracture risk; those who had a kidney transplant between the start of dialysis and their first PTH measurement (to exclude those who were not receiving dialysis at the time of study entry). Patients were followed for 3 years or until first fracture, death, or emigration from the province (emigration occurs in around 0.2% of patients per year).[30]

3.2.4 Patient Characteristics

We captured demographics and comorbidities in the 5-year period before the index date, laboratory values in the one-year period before the index date, and medications in the 180-day period before the index date, with the exception of bisphosphonate, denosumab, and steroid use, which were captured in the 5-year period before the index date due to a prolonged effect on bone quality. Codes used to capture baseline characteristics are

presented in Appendix A.C and codes used to capture medication use are shown in Appendix A.D.

3.2.5 Outcomes

The primary outcome was major osteoporotic fracture. Fracture sites included hip/femur, pelvis, wrist/forearm, shoulder/upper arm, and spine. We used an algorithm for fracture that has been used in several research studies.[31,32] We chose to report predicted fracture risk at 1 and 3 years to provide patients and clinicians with a clinically relevant, short to medium-term prognosis, given that the 3-year risk of mortality in patients receiving dialysis is approximately 30%.[33]

3.2.6 Statistical Analysis

Baseline characteristics for the cohort were summarized using descriptive statistics. Continuous measures were expressed as means (standard deviation) or medians (25^{th}, 75^{th} percentile) and categorical measures were expressed as frequency (proportions). The 1-year and 3-year incidence of any fracture, and the 3-year incidence of fracture at each site was obtained from the cumulative incidence functions directly accounting for the competing risk of death.

The clinical prediction tool for fracture was generated with a set of predictors that were identified *a priori* from the literature as being associated with fracture, and that were available in our datasets. Serum magnesium and vitamin D3 concentration were excluded due to a high degree of missingness (47.7% and 90.4% respectively). The remainder of missing values were imputed using the fully conditional specification (FCS) method, assuming the data were missing at random. Variables shown to be closely correlated with missingness or with the value of the missing variables were included in the imputation model. The Fine and Grey subdistribution hazards model was used for fracture prediction, accounting for the competing risk of death using the *riskRegression* package in R statistical software.[34–37] After an initial model containing all candidate predictors was evaluated, successive models were built with variables removed based on low statistical significance or difficulty with obtaining the variable in clinical practice. Models were compared using the Akaike Information Criterion (AIC), the Bayesian Information

Criterion (BIC) Brier Score, and the time dependent area under the curve (AUC). Models were internally validated using 10-fold cross validation.[37] The linearity assumption was tested by the inclusion of restricted cubic splines and the proportional hazards assumption, by the inclusion of a time-varying covariate in the model; (a p-value of <0.05 was considered to be a significant violation of the linearity or proportional hazards assumptions).[38] Outliers were assessed by examination of continuous variables for clinically implausible values.

3.3 Results

3.3.1 Baseline Characteristics

We identified 11,599 individuals receiving dialysis who had an available serum PTH value between January 1st 2010 and December 31st 2017. Details on the full cohort build are shown in Appendix A.E. Selected baseline characteristics are shown in Table 1. Patients receiving dialysis were, on average, 66 years of age (SD 12 years) and 38.6% were female. Overall, 12.1% of individuals had a history of fracture in the prior 5 years, with 2.6% of fractures occurring in the year before cohort entry. In this cohort, 37.8% of individuals were new to maintenance dialysis (i.e., had a dialysis vintage of less than 6 months); the median dialysis vintage was 0.8 years (25th percentile, 75th percentile, 0.4, 2.5). At the time of cohort entry, bisphosphonates and denosumab were uncommonly prescribed in the past (4.0% and 0.2% of patients, respectively, and) but 27.0% and 4.8% of individuals respectively, used proton pump inhibitors and steroids. Activated vitamin D was used by 28.5% of patients.

Approximately 23.7% of individuals were missing at least one serum laboratory value of albumin, calcium, or phosphate in the preceding year. The most common pattern was that patients were missing all three of calcium, albumin and phosphate (18.9% of the overall cohort- see Appendix A.F). This is likely because some hospitals do not provide lab values to OLIS. Patients who had only PTH measured at a community laboratory would be included in the cohort regardless of whether the hospital through which they received dialysis provided laboratory values to OLIS.[28] The most recent lab measurements for albumin and phosphate were available a median of 35 days (IQR 11-59) before the index

date, and the most recent measurement for calcium was available 36 days (IQR: 9-63) before the index date. Less than six patients were excluded from the cohort due to an implausibly high PTH level (>1,000 pmol/L).

Patients were followed for an average of 2.4 years (SD 0.95). The most common reason for early end of follow up was death (4,200 patients), followed by emigration from the province (328 patients). At three years, the cumulative incidence of death was 33.5% (95% CI 32.6, 34.3). After 3 years, 839 fractures occurred with a cumulative incidence of 7.4% (95% CI 6.9, 7.9%), corresponding to an event rate of 31.5 fractures per 1000 person-years. The most common fracture site was at the hip, followed by the pelvis (see Table 2).

3.3.2 Prediction Model and Validation

The final prediction model included the following variables: age, sex, prior kidney transplant, previous fracture, proton pump inhibitor use within 90 days, most recent concentration of parathyroid hormone and albumin (Table 3). The time dependent AUC for the cross validated final model was compared to the full model (which also included vitamin D use within 90 days, steroid use within 90 days, dialysis vintage, a history of diabetes, rheumatoid arthritis, chronic liver disease, blood calcium and phosphate values). The time dependent AUC for the cross-validated final and full models can be found in Table 4. The AICs were comparable for these models, suggesting that there was minimal additional information added by including extra variables (i.e., 15293 vs 15286 for the final and full models, respectively). The final model was chosen since it contains fewer laboratory values and comorbidities, making it easier to implement and to minimize the risk of overfitting, while providing similar estimates of AUC at 1-year and 3-years.

The predicted risks of fracture in the final model at 1 and 3 years ranged from 0.2-8.5% and 1.1-34.7% respectively, with a median predicted risk of 0.6% and 2.8% at 1 and 3 years respectively. The final model showed good calibration from predicted risks of 0-5% (see Figure 1).

Assumptions of the Fine-Gray subdistribution hazard were tested for each variable in the final model. The splined terms for both PTH and age were found to be statistically significant, indicating that they violated the linearity assumption. Thus, the final model included these non-linear variables using restricted cubic splines. History of kidney transplant and age were found to violate the proportional hazards assumption. The non-proportionality observed with age was mitigated when it was modelled non-linearly. Visual examination of the cumulative incidence function stratified by transplant status, did not show any crossing lines (Appendix A.H) therefore, the variable was left as a fixed variable for parsimony. The effect of transplant status can be interpreted as an average of the effect over the full three-year period.

3.3.3 Clinical Utility of the Prediction Model

The sensitivity and specificity of the final model in identifying those at high risk of future fracture is shown in Appendix A.I. The sensitivity for predicting fracture at 3 years ranged from 32% to 65% with a specificity from 87% to 58% based on risk cutoffs ranging between 5% and 3%, respectively. The sensitivity to predict fracture at one year ranged from 15-87% with a specificity ranging from 98%-35% for cutoffs ranging from 2%-0.5% respectively.

3.3.4 Sensitivity Analyses

A complete case analysis yielded similar time dependent AUCs at both 1 and 3 years compared to final model using imputed values (see Table 4). Additionally, a cause specific hazards model, treating death as a censoring event performed similarly. A model with hip fracture as the outcome also had similar discrimination.

3.4 Discussion

In a cohort of over 11,000 individuals receiving maintenance dialysis, rates of fracture were 31.5 per 1000 patient-years, consistent with rates previously described in the literature both in Canada and internationally.[2,39,40] A prediction model for fracture using routinely collected data was developed and demonstrated to perform well, with the best

performance at 1 year. This calculator will be presented in an electronic form on QxCalculate in the near future.

We found that older age, female sex and previous fractures had a strong impact and predicted a higher risk of fracture in patients receiving dialysis, which is similar to the general population.[1,12,23,41–46] Further, both lower and higher values of PTH were associated with an increased risk of fracture in the dialysis population, which has been seen in two previous studies, and may explain a lack of association with fracture in previous studies that modelled PTH linearly.[15,39,44,45,47–49]

When compared to a longitudinal study of FRAX (without BMD) applied to patients receiving maintenance hemodialysis with a 2-year follow-up, the prediction model performed similarly (AUC 0.76 at 2 years vs 0.78 at 1 year and 0.72 at 3 years in our study).[24] Cross sectional studies of prevalent fracture in patients receiving dialysis, including one conducted in Manitoba, Canada, also demonstrated similar AUCs or c-statistics to our model, despite ours predicting fracture at 3 years rather than prevalent fracture.[17,25,27] Our fracture risk prediction model also does not require any input beyond routinely collected data and could be easily implemented at the bedside. For example, FRAX requires information on a parental history of hip fracture and the patient's bone mineral density result, both of which may be difficult to obtain in older, frail individuals receiving dialysis. Furthermore, information on smoking and alcohol use are also required, which would preclude its use for research using administrative data where this information is typically not available. Whereas other fracture prediction tools were designed to predict a patient's long-term risk of fracture (i.e.. 10 years), our tool was designed to predict a patient's 1- and 3-year risk of fracture, which may be more clinically meaningful for those receiving dialysis because the 5-year risk of mortality in these patients is 48%.[33] While FRAX accounts for the competing risk of death, mortality rates in the general population are much lower than for patients receiving dialysis, and therefore, the FRAX tool may over-estimate the risk of fracture in patients receiving dialysis.[50]

Compared to other models that used BMD measurements alone to predict fracture, our model performed similarly to one study and better than two others that examined several different sites of fracture.[12,17,27] Only one study found that BMD at the ultradistal radius had better discriminatory power to detect non-spine fractures than the fracture prediction model presented above (AUC 0.86); however, that study was limited by a small sample size (13 non-spine fractures overall).[14]

We would recommend a 3-year risk of fracture of ≥4% as the threshold for consideration of treatment in patients receiving dialysis as this has reasonable specificity (78%), particularly considering the relatively high risk of side effects with current osteoporosis therapies in dialysis. However, other factors should also be considered when making treatment decisions including functional status, anticipated life expectancy, and the availability of potential treatments.

3.4.1 Strengths and Limitations

Our study has several strengths. We were able to include a large number of patients receiving dialysis and follow them for 3 years with minimal loss to follow-up. We observed over 800 fractures and expect that there is a low risk of overfitting or optimism in the developed prediction model. The longitudinal nature of the study and the inclusion of both incident and prevalent patients receiving dialysis also allows the model to be applied as a predictive tool in a broad population of patients receiving dialysis. Similarly, the use of routinely collected data, rather than a traditional trial results in the inclusion of older, more comorbid individuals receiving dialysis, making the fracture risk prediction tool more clinically relevant in usual care.[51] Finally, we only included predictors from the patient's medical history or laboratory values that are currently obtained as the standard of care in patients receiving dialysis, making the tool easy to implement.

There are also several limitations. A just over half of patients receiving dialysis were excluded from the cohort due to no PTH test results in the year prior. Similarly, approximately 20% of the cohort was missing a value for serum calcium, albumin, or phosphate; the availability of this data may have improved the model performance. There are several potential explanations for the proportion of missingness. Some hospitals in

Ontario did not contribute laboratory values to OLIS, particularly in the earlier years of this study. For example, in 2017, 38.6% of the Ontario population lived in a catchment area where the hospital did not contribute to OLIS.[28] Given that patients receiving dialysis have bloodwork taken during their treatments, which are typically received in a hospital, it is possible that many of these individuals' bloodwork was not available. We do not expect these individuals to vary importantly from the rest of the dialysis population. Alternatively, individuals with little pre-dialysis nephrology care or who are frail and admitted to hospital frequently may miss opportunities to have their PTH (and other renal related labs) ordered. The exclusion of these individuals may have biased the cohort towards a healthier population, limiting its application to sicker individuals. However, frail individuals with frequent hospitalizations may have a shorter life expectancy, and therefore, the benefit of initiating and pharmacologic treatments to reduce fracture, such as denosumab, is not as clear. An additional limitation is that we were unable to include other common fracture risk factors including BMD and body mass index, as they were not available in our databases. However, their exclusion makes this risk score amenable to use in pragmatic or administrative research, as it does not require any additional measurements.

3.4.2 Conclusions

We present an easy-to-use fracture risk prediction score which discriminates well between those who will and will not fracture a bone at 1 and 3 years. We will present this tool using a widely used medical calculation interface (QxCalculate). This can be used both clinically as well as in research settings to identify those who could be included in a clinical trial for therapies. Further research is needed, including external validation of the score as well as further identification of therapies to reduce the risk of fracture in individuals receiving dialysis.

Funding: This study was conducted under the auspices of the ICES Kidney Dialysis Transplantation Program at ICES Western who are supported by a grant from the Canadian Institutes of Health Research (CIHR). ICES is funded by an annual grant from the Ontario Ministry of Health (MOH) and Ministry of Long-Term Care (MLTC). Core funding for ICES Western is provided by the Academic Medical Organization of

Southwestern Ontario (AMOSO), the Schulich School of Medicine and Dentistry (SSMD), Western University, and the Lawson Health Research Institute (LHRI). Dr. Cowan is supported by the Western University Department of Medicine R Parts of this material are based on data and information compiled and provided by Ministry of Health (MOH), CIHI, and Ontario Health (OH). The analyses, conclusions, opinions, and statements expressed herein are solely those of the authors and do not reflect those of the funding or data sources; no endorsement is intended or should be inferred. Parts of this material are also based on data and information compiled and provided by the Canadian Institutes of Health Information (CIHI). We thank IQVIA Solutions Canada Inc. for use of their Drug Information File. The analyses, conclusions, opinions, and statements expressed herein are solely those of the authors and do not reflect those of the funding or data sources; no endorsement is intended or should be inferred. The study sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

3.5 References

1. Alem AM, Sherrard DJ, Gillen DL, et al. Increased risk of hip fracture among patients with end-stage renal disease. *Kidney Int*. 2000;58(1):396-399. doi:10.1046/j.1523-1755.2000.00178.x

2. Naylor KL, McArthur E, Leslie WD, et al. The three-year incidence of fracture in chronic kidney disease. *Kidney Int*. 2014;86(4):810-818. doi:10.1038/ki.2013.547

3. Coco M, Rush H. Increased incidence of hip fractures in dialysis patients with low serum parathyroid hormone. *American Journal of Kidney Diseases*. 2000;36(6):1115-1121. doi:10.1053/ajkd.2000.19812

4. Mittalhenkle A, Gillen DL, Stehman-Breen CO. Increased risk of mortality associated with hip fracture in the dialysis population. *American Journal of Kidney Diseases*. 2004;44(4):672-679. doi:10.1053/j.ajkd.2004.07.001

5. Downey C, Kelly M, Quinlan JF. Changing trends in the mortality rate at 1-year post hip fracture - a systematic review. *World J Orthop*. 2019;10(3):166-175. doi:10.5312/wjo.v10.i3.166

6. Beaubrun AC, Kilpatrick RD, Freburger JK, Bradbury BD, Wang L, Brookhart MA. Temporal trends in fracture rates and postdischarge outcomes among hemodialysis patients. *Journal of the American Society of Nephrology*. 2013;24(9):1461-1469. doi:10.1681/ASN.2012090916

7. Nair SS, Mitani AA, Goldstein BA, Chertow GM, Lowenberg DW, Winkelmayer WC. Temporal trends in the incidence, treatment, and outcomes of hip fracture in older patients initiating dialysis in the United States. *Clinical Journal of the American Society of Nephrology*. 2013;8(8):1336-1342. doi:10.2215/CJN.10901012

8. Lo LWT, Yanling X, Chou ACC, Howe T Sen, Allen JC, Koh JSB. End-stage renal failure is an independent risk factor for 1-year mortality after hip fracture surgery. *Geriatr Orthop Surg Rehabil*. 2018;9. doi:10.1177/2151459318770561

9. Cowan A, Jeyakumar N, Ouédraogo AM, et al. The Incidence of Hypocalcemia After Denosumab Administration in Patients with CKD. In: *American Society of Nephrology Kidney Week*. ; 2021.

10. Robinson DE, Ali MS, Pallares N, et al. Safety of Oral Bisphosphonates in Moderate-to-Severe Chronic Kidney Disease: A Binational Cohort Analysis. *Journal of Bone and Mineral Research*. 2021;36(5):820-832. doi:10.1002/jbmr.4235

11. Cosman F, Crittenden DB, Ferrari S, et al. FRAME Study: The Foundation Effect of Building Bone With 1 Year of Romosozumab Leads to Continued Lower Fracture Risk After Transition to Denosumab. *Journal of Bone and Mineral Research*. 2018;33(7):1219-1226. doi:10.1002/jbmr.3427

12. Iimori S, Mori Y, Akita W, et al. Diagnostic usefulness of bone mineral density and biochemical markers of bone turnover in predicting fracture in CKD stage 5D patients-a

single-center cohort study. *Nephrology Dialysis Transplantation*. 2012;27(1):345-351. doi:10.1093/ndt/gfr317

13. Jamal SA, Gilbert J, Gordon C, Bauer DC. Cortical PQCT measures are associated with fractures in dialysis patients. *Journal of Bone and Mineral Research*. 2006;21(4):543-548. doi:10.1359/jbmr.060105

14. Yamaguchi T, Kanno E, Tsubota J, Shiomi T, Nakai, M, Hattori S. Retrospective Study on the Usefulness of Radius and Lumbar Bone Density in the Separation of Hemodialysis Patients with Fractures from Those Without Fractures. Vol 19.; 1996.

15. Ureña P, Bernard-Poenaru O, Ostertag A, et al. Bone mineral density, biochemical markers and skeletal fractures in haemodialysis patients. *Nephrology Dialysis Transplantation*. 2003;18(11):2325-2331. doi:10.1093/ndt/gfg403

16. Jamal SA, Hayden JA, Beyene J. Low Bone Mineral Density and Fractures in Long-Term Hemodialysis Patients: A Meta-Analysis. *American Journal of Kidney Diseases*. 2007;49(5):674-681. doi:10.1053/j.ajkd.2007.02.264

17. Jafari M, Anwar S, Kour K, Sanjoy S, Goyal K, Prasad B. T Scores, FRAX, Frailty Phenotype, Falls, and Its Relationship to Fractures in Patients on Maintenance Hemodialysis. *Can J Kidney Health Dis*. 2021;8:205435812110411. doi:10.1177/20543581211041184

18. Prasad B, Ferguson T, Tangri N, Ng CY, Nickolas TL. Association of Bone Mineral Density With Fractures Across the Spectrum of Chronic Kidney Disease : The Regina CKD-MBD Study. *Can J Kidney Health Dis*. 2019;6:1-10. doi:10.1177/2054358119870539

19. PARISIEN M, SILVERBERG SJ, SHANE E, et al. The Histomorphometry of Bone in Primary Hyperparathyroidism: Preservation of Cancellous Bone Structure*. *J Clin Endocrinol Metab*. 1990;70(4):930-938. doi:10.1210/jcem-70-4-930

20. Ketteler M, Block GA, Evenepoel P, et al. Executive summary of the 2017 KDIGO Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD) Guideline Update:

what's changed and why it matters. *Kidney Int*. 2017;92(1). doi:10.1016/j.kint.2017.04.006

21. Papaioannou A, Morin S, Cheung AM, et al. 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: Summary. *CMAJ*. 2010;182(17):1864-1873. doi:10.1503/cmaj.100771

22. Naylor KL, Garg AX, Zou G, et al. Comparison of fracture risk prediction among individuals with reduced and normal kidney function. *Clinical Journal of the American Society of Nephrology*. 2015;10(4):646-653. doi:10.2215/CJN.06040614

23. Whitlock RH, Leslie WD, Shaw J, et al. The Fracture Risk Assessment Tool (FRAX®) predicts fracture risk in patients with chronic kidney disease. *Kidney Int*. 2019;95(2):447-454. doi:10.1016/j.kint.2018.09.022

24. Przedlacki J, Buczyńska-Chyl J, Koźmiński P, et al. The utility of FRAX® in predicting bone fractures in patients with chronic kidney disease on hemodialysis: a two-year prospective multicenter cohort study. *Osteoporosis International*. 2018;29(5):1105-1115. doi:10.1007/s00198-018-4406-z

25. Jirasirirak S, Disthabanchong S, Ongphiphadhanakul B, Arj-Ong Vallibhakara S, Nimitphong H. Prevalence and predictors of asymptomatic vertebral fracture in patients with end-stage renal disease. *Heliyon*. 2022;8(3). doi:10.1016/j.heliyon.2022.e09158

26. Przedlacki J, Buczyńska-Chyl J, Koźmiński P, et al. FRAX prognostic and intervention thresholds in the management of major bone fractures in hemodialysis patients: A two-year prospective multicenter cohort study. *Bone*. 2020;133. doi:10.1016/j.bone.2019.115188

27. Chang A j., Ying Q, Chen X n., Wang W m., Chen N. Evaluation of three risk assessment tools in discriminating fracture status among Chinese patients undergoing hemodialysis. *Osteoporosis International*. 2016;27(12):3599-3606. doi:10.1007/s00198-016-3690-8

28. Iskander C, McArthur E, Nash DM, et al. Identifying Ontario geographic regions to assess adults who present to hospital with laboratory-defined conditions: a descriptive study. *CMAJ Open*. 2019;7(4):E624-E629. doi:10.9778/cmajo.20190065

29. Kettler M, Leonard MB, on behalf of the Work Group. KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD). Published 2017. Accessed October 7, 2022. https://kdigo.org/guidelines/ckd-mbd/

30. Finance OM of. Ontario Population Projections, 2018–2046. Queen's Printer for Ontario. Published 2019. Accessed February 11, 2020. https://www.fin.gov.on.ca/en/economy/demographics/projections/#s3b

31. Papaioannou A, Kennedy CC, Ioannidis G, et al. Comparative trends in incident fracture rates for all long-term care and community-dwelling seniors in Ontario, Canada, 2002–2012. *Osteoporosis International*. 2016;27(3):887-897. doi:10.1007/s00198-015-3477-3

32. O'Donnell S. Use of administrative data for national surveillance of osteoporosis and related fractures in Canada: Results from a feasibility study. *Arch Osteoporos*. 2013;8(1-2). doi:10.1007/s11657-013-0143-2

33. Ontario Renal Network. Discussing Prognosis with Patients on Dialysis. https://www.ontariorenalnetwork.ca/sites/renalnetwork/files/assets/discussingprognosis.pdf.

34. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. Published 2022. https://www.R-project.org/

35. Gerds T, Ohlendorff J, Ozenne B. _riskRegression: Risk Regression Models and Prediction Scores for Survival Analysis with Competing Risks_. R package version 2023.03.22. Published 2023. <https://CRAN.R-project.org/package=riskRegression>.

36. Gerds TA, Kattan MW. *Medical Risk Prediction: With Ties to Machine Learning*. Chapman and Hall/CRC; 2021. doi:10.1201/9781138384484

37. Zhang Z, Cortese G, Combescure C, et al. Overview of model validation for survival regression model with competing risks using melanoma study data. *Ann Transl Med*. 2018;6(16):325-325. doi:10.21037/atm.2018.07.38

38. Bellera CA, Macgrogan G, Debled M, Tunon De Lara C, Brouste V, Mathoulin-Pélissier S. *Variables with Time-Varying Effects and the Cox Model: Some Statistical Concepts Illustrated with a Prognostic Factor Study in Breast Cancer*.; 2010. http://www.biomedcentral.com/1471-2288/10/20

39. Jadoul M, Albert JM, Akiba T, et al. Incidence and risk factors for hip or other bone fractures among hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study. *Kidney Int*. 2006;70(7):1358-1366. doi:10.1038/sj.ki.5001754

40. Iseri K, Carrero JJ, Evans M, et al. Major fractures after initiation of dialysis: Incidence, predictors and association with mortality. *Bone*. 2020;133. doi:10.1016/j.bone.2020.115242

41. Iseri K, Watanabe M, Yoshikawa H, et al. Effects of Denosumab and Alendronate on Bone Health and Vascular Function in Hemodialysis Patients: A Randomized, Controlled Trial. *Journal of Bone and Mineral Research*. 2019;34(6):1014-1024. doi:10.1002/jbmr.3676

42. Adachi JD, Brown JP, Schemitsch E, et al. Fragility fracture identifies patients at imminent risk for subsequent fracture: real-world retrospective database study in Ontario, Canada. *BMC Musculoskelet Disord*. 2021;22(1). doi:10.1186/s12891-021-04051-9

43. Wakasugi M, Kazama JJ, Taniguchi M, et al. Increased risk of hip fracture among Japanese hemodialysis patients. *J Bone Miner Metab*. 2013;31(3):315-321. doi:10.1007/s00774-012-0411-z

44. Kaneko TM, Foley RN, Gilbertson DT, Collins AJ. Clinical epidemiology of long-bone fractures in patients receiving hemodialysis. *Clin Orthop Relat Res*. 2007;457:188-193. doi:10.1097/BLO.0b013e318031465b

45. Stehman-Breen CO, Sherrard DJ, Alem AM, et al. Risk factors for hip fracture among patients with end-stage renal disease. *Kidney Int*. 2000;58(5):2200-2205. doi:10.1111/j.1523-1755.2000.00394.x

46. Ball AM, Gillen DL, Sherrard D, et al. *Risk of Hip Fracture Among Dialysis and Renal Transplant Recipients*.; 2002. https://jamanetwork.com/

47. Danese MD, Fox KM, Duryea JL, Desai P, Rubin RJ. The rate, cost and outcomes of parathyroidectomy in the united states dialysis population from 2016–2018. *BMC Nephrol*. 2022;23(1). doi:10.1186/s12882-022-02848-x

48. Kaji H, Suzuki M, Yano S, et al. *Risk Factors for Hip Fracture in Hemodialysis Patients*. Vol 22.; 2002. www.karger.com

49. Inaba M, Okuno S, Kumeda Y, Yamakawa T, Ishimura E, Nishizawa Y. Increased incidence of vertebral fracture in older female hemodialyzed patients with type 2 diabetes mellitus. *Calcif Tissue Int*. 2005;76(4):256-260. doi:10.1007/s00223-004-0094-0

50. Ramspek CL, Teece L, Snell KIE, et al. Lessons learnt when accounting for competing events in the external validation of time-To-event prognostic models. *Int J Epidemiol*. 2022;51(2):615-625. doi:10.1093/ije/dyab256

51. Smyth B, Haber A, Trongtrakul K, et al. Representativeness of Randomized Clinical Trial Cohorts in End-stage Kidney Disease: A Meta-analysis. *JAMA Intern Med*. 2019;179(10):1316-1324. doi:10.1001/jamainternmed.2019.1501

Table 3.1 Selected Baseline Characteristics

Baseline Characteristics	All Patients N=11,599
Demographics, n (%)	
Age, mean (SD), years	66.18 (12.33)
	67 (57-76)
Female	4,480 (38.6)
Long Term Care	1,632 (14.1)
Comorbidities, n (%)	
Dialysis Vintage (years)	
Mean (SD)	2.1 (3.3)
Median (25th percentile, 75th percentile)	0.81 (0.4,2.5)
0-1 years	6,268 (54.0)
1-2 years	1,772 (15.3)
2-3 years	1161 (10.0)
>3 years	>2,392 (20.7)
missing	<6 (0.0)
Charlson Comorbidity Index	
Mean (SD)	3.52 (1.74)
Median (25th percentile, 75th percentile)	3 (2,5)
Prior fracture (in the prior year)	
All Fractures	304 (2.6)
Hip	111 (1.0)
Spine	44 (0.4)
Shoulder or Humerus	49 (0.4)
Wrist or Forearm	75 (0.6)
Pelvic	79 (0.7)
Prior fracture (any time in available records)	
All Fractures	1,403 (12.1)
Hip	374 (3.2)
Spine	200 (1.7)
Shoulder or Humerus	327 (2.8)
Wrist or Forearm	612 (5.3)
Pelvic	280 (2.4)
Previous Transplant	280 (2.4)
Cause of ESRD	
Cystic	630 (5.4)
Diabetes	4,847 (41.8)
GN	1,579 (13.6)

Missing	143 (1.2)
Other	2,557 (22.0)
Vascular	1,843 (15.9)
Liver Disease	1,381 (11.9)
Diabetes	7,433 (64.1)
Rheumatoid Arthritis	287 (2.5)
Medication Use n (%) (over previous 5 years unless otherwise specified)*	
Universal Prescription Drug Benefit Eligible	9,963 (85.9)
Number of Unique Drug Names	
Mean (SD)	7.51 (7.95)
Median (25th percentile, 75th percentile-Q3)	7 (0,14)
Bisphosphonates**	461 (4.0)
Denosumab**	21 (0.2)
Steroids (5-year history)	2,216 (19.1)
Steroids (90 days)	555 (4.8)
Proton Pump Inhibitor	3,128 (27.0)
Activated vitamin D	3,307 (28.5)
Laboratory Testing	
PTH (pmol/L)	
Mean (SD)	43.57 (46.96)
Median (25th percentile, 75th percentile)	30 (16,55)
Albumin (g/L)	
Mean (SD)	35.35 (5.27)
Median (25th percentile, 75th percentile)	36 (32,39)
missing - n (%)	2,325 (20.0)
Days drawn prior to index date, median (25th percentile, 75th percentile)	35 (28, 52)
Calcium (mmol/L)	
Mean (SD)	2.35 (0.20)
Median (25th percentile, 75th percentile)	2 (2,2)
missing - n (%)	2,671 (23.0)
Days drawn prior to index date, median (25th percentile, 75th percentile)	36 (28, 55)
Phosphate (mmol/L)	
Mean (SD)	1.60 (0.49)
Median (25th percentile, 75th percentile)	2 (1, 2)
missing - n (%)	2,412 (20.8)
Days drawn prior to index date, median (25th percentile, 75th percentile)	35 (28, 52)
Magnesium (mmol/L)	

Mean (SD)	0.86 (0.17)
Median (25th percentile, 75th percentile)	1 (1,1)
missing - n (%)	5,527 (47.7)
25 hydroxy vitamin D (nmol/L)	
Mean (SD)	52.24 (29.08)
Median (25th percentile, 75th percentile)	47 (31,67)
missing - n (%)	10,491 (90.40)

SD: Standard deviation; ODB: Ontario Drug Benefit; PTH: parathyroid hormone
* Of the total cohort, 9,963 patients had available prescription medication information. The percentages listed here assume that the remainder were not taking the medication of interest
** denosumab or bisphosphonate use was collected from 1-5 years prior to the index date as their use within 1 year of the index date was considered an exclusion

Table 3.2 Incidence of Fracture in the Cohort

	Number of events	Event Rate per 1000 py	Cumulative Incidence at 3 years (95%CI)
All Fractures (3 years)	839	31.5	7.36 (6.89, 7.85)
Hip fracture (3 years)	299	11.0	2.62 (2.34, 2.93)
Spine fracture (3 years)	155	5.7	1.36 (1.16, 1.59)
Shoulder or humerus (3 years)	131	4.8	1.15 (0.97, 1.36)
Wrist or forearm (3 years)	220	8.1	1.93 (1.69, 2.20)
Pelvis (3 years)	245	9.0	2.15 (1.89, 2.43)
Death (3 years)	3180	143.2	33.5 (32.6, 34.3)
All Fractures (1 year)	367	34.8	2.93 (2.62, 3.26)

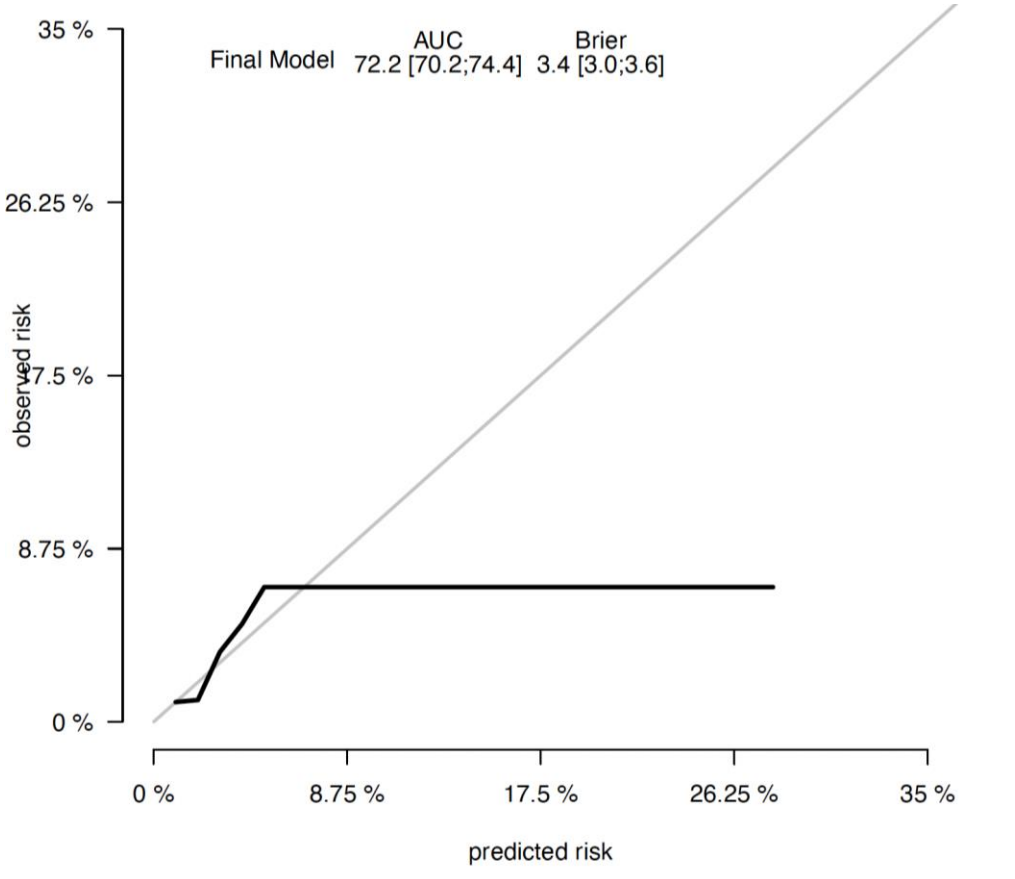


Figure 3.1 Three-year Calibration Curve for the Final Model

Table 3.3 Final Fracture Risk Prediction Model

Variable	HR (95% CI)
Age	*
Female Sex	1.46 (1.27, 1.67)
Renal transplant	1.34 (0.87, 2.05)
Previous Fracture >1 year	1.65 (2.37, 2.00)
Previous fracture <1 year	3.63 (2.86, 4.60)
Baseline PPI use	1.23 (1.04, 1.45)
PTH (pmol/L)	*
Albumin (g/L)	0.99 (0.98, 1.00)

** These variables are non-linear and include splined terms. Please see Appendix A.G for a graphical representation of the HR.

Table 3.4 Time Dependent AUC of Differing Models at 1 and 3 Years

Model	1 year AUC (95% CI)	3 year AUC (95% CI)
Final Model	78.8 (75.3, 83.8)	72.2 (70.4, 74.4)
Full Model	77.7 (73.3,84.4)	69.9 (68.0,72.2)
Hip Fracture	80.1 (77.0,83.5)	71.9 (70.1,74.2)
Cause Specific Hazards	79.5 (75.7, 84.0)	71.6 (69.6,73.3)
Complete Case Analysis	77.7 (73.6,83.0)	70.8 (68.6, 72.7)
*AUC obtained using 10-fold cross validation		

Chapter 4

4 Fracture Risk of Sodium Glucose Cotransporter-2 Inhibitors in Chronic Kidney Disease

Cowan, Andrea[1,3], Jeyakumar, Nivethika[1], Kang, Yuguang[1], Dixon, Stephanie N.[1,2,4], Garg, Amit X.[1,2,3,4], Naylor, Kyla[1], Weir, Matthew A.[1,3,4]Clemens, Kristin K.[1,2,3,4,5]

1. ICES, ON, Canada
2. Department of Epidemiology & Biostatistics, Western University, London ON, Canada
3. Department of Medicine, Western University, London ON, Canada
4. Lawson Health Research Institute, London ON, Canada
5. St. Joseph's Health Care London, London ON, Canada

4.1 Introduction

Due to their proven cardio- and reno-protective benefits, sodium glucose transporter-2 inhibitors (SGLT-2i) are now recommended in all patients with diabetic kidney disease who have an estimated glomerular filtration rate (eGFR) ≥30/min/1.73m^2.[1–4] However, in some large trials, their use has been reported to increase the risk of skeletal fracture. For example, the CANVAS trial (n=10,142), found that canagliflozin was associated with a higher risk of fractures than placebo (15.4 versus 11.9 fractures per 1000 patient years respectively, p=0.02).[1] This led the United States Food and Drug Administration and Health Canada to issue a "warning and precaution" about fracture risk on canagliflozin's product monograph.[5,6] A subsequent meta-analysis of 9 randomized controlled trials also found a higher risk of fracture with SGLT-2i, compared to placebo or active control, although CANVAS participants made up over half of the included individuals and drove this positive finding.[7]

There are two proposed mechanisms for SGLT-2i induced fractures: a higher risk of falls through volume depletion or hypoglycemia; and a decrease in bone quality through weight loss, increased bone turnover and disturbed calcium phosphate balance.[8–13] Patients with chronic kidney disease (CKD) might be particularly susceptible to changes

in bone quality due to a predisposition to the metabolic derangements of CKD-mineral bone disorder.[14] A unique feature of the CANVAS population was that participants had a lower baseline eGFR when compared to other SGLT-2i studies (16% of CANVAS participants had an eGFR < 60 ml/min/1.73m^2 compared to 9% of other study participants included in the meta-analysis).[15] This raises the possibility that patients with CKD may be at a greater risk of SGLT-2i associated fractures.[7] Supporting this finding was a small study of dapagliflozin in patients with CKD (all with eGFR <60ml/min/1.73m^2), which also found a higher risk of fracture over placebo.[9] Subsequent studies that concluded that SGLT-2i do not alter fracture risk did not specifically examine patients with CKD. [16–23] Skeletal fractures are of particular importance in the CKD population as they are associated with a higher risk of mortality compared to those with normal kidney function, even in those with an eGFR <45 ml/min/1.73m^2.[24]

We conducted this population-based study of older adults to determine the 180- and 365-day risk of fracture associated with starting a SGLT-2i versus a dipeptidyl peptidase-4 inhibitor (DPP-4i) with a special focus on heterogeneity by eGFR. We selected DPP-4i as a comparator drug to reduce confounding by indication because, like SGLT-2i, DPP-4i are also frequently used in addition to insulin or metformin for diabetes management. Unlike SGLT-2i, they have no known risk of fracture.[25,26] We hypothesized that if a higher risk of fracture was observed with SGLT-2i versus DDP-4i, the risk would be greatest in patients with advanced CKD.

4.2 Methods

4.2.1 Study Design and Setting

We conducted a population-based cohort study of older adults aged 66 years or older, in Ontario, Canada using linked administrative health data. All Ontario residents (~14 million) have universal access to insured hospital and physician services. Residents over 65 years of age (~2.2 million) also receive universal prescription-drug coverage. [27] The use of data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act and the Research Ethics Board did not require additional review. In this study we followed the Reporting of studies Conducted using Observational

Routinely collected health Data guidelines for PharmacoEpidemiology (RECORD-PE) studies using healthcare databases.[28] (see Appendix A).

4.2.2 Data Sources

Patient characteristics, prescription drug use, covariate information and outcome data were obtained from eight health databases at ICES (ices.on.ca). Detailed information on these datasets and variables used in this study can be found in Appendix B and C respectively. These datasets were linked using unique encoded identifiers and analyzed at ICES Western. Less than 0.2% of patients in this study would be expected to emigrate from the province each year, which was the only reason for lost to follow-up.[27]

4.2.3 Population

We created a cohort of older adults (≥66 years) in Ontario who were new, outpatient users of an SGLT-2i (canagliflozin, empagliflozin or dapagliflozin) or DPP4-i (saxagliptin, sitagliptin or linagliptin) between July 1, 2015 (the earliest date of universal provincial coverage of SGLT-2i) [29] and September 30th, 2019.

New use was defined as having no evidence of a prescription for either medication class in the preceding 180 days. The dispensing date of the first eligible prescription was considered the cohort entry or index date. Drug identification numbers used to identify SGLT-2i and DPP-4i prescriptions are listed in Appendix D.

After standard data cleaning, we excluded the following patients: <66 years of age (to allow a full 1 year lookback for baseline medication use); patients prescribed concurrent SGLT-2i and DPP4-i (to ensure mutually exclusive groups); patients with more than one prescription for the same medication class on the index date, patients with unusual study drug doses (to exclude atypical prescription patterns), and patients discharged from hospital in the two days prior to filling the prescription (as those patients who start treatment in hospital will typically fill prescriptions shortly after discharge). We also excluded individuals with no evidence of serum creatinine measurement in the year prior, and those with an eGFR <30 ml/min/1.73m^2 or receiving dialysis (as SGLT-2i were contraindicated in this group over the study period).

4.2.4 Patient Characteristics

We captured demographics and comorbidities in the preceding five years, and health care utilization, medication use and laboratory testing in the preceding one year. Codes used to capture baseline characteristics are presented in Appendix C.

We determined kidney function based on the most recent eGFR in the year prior to index date. Serum creatinine values were used to calculate the eGFR using the Chronic Kidney Disease Epidemiology (CKD-EPI) equation.[30–33] As per recent Ontario Renal Network guidelines, race was not included in the eGFR calculation.[34]

Continuous use of SGLT-2i and DPP-4i was defined as consecutive prescription claims for the same drug within a period equivalent to 150% of the days supplied for the previous prescription.[35] For example, if an individual was given a 30-day prescription and renewed it within 45 days this would be counted as continuous use.

4.2.5 Outcomes

Our primary outcome was a hospital encounter (hospitalization or emergency department visit) for fragility fracture (hip, spine, shoulder/upper arm, forearm/wrist and pelvis) within 180 days of a new prescription for an SGLT-2i or DPP-4i. We used an algorithm for fracture which has been used in several previous research studies from our region (See Appendix E).[36,37] We chose 180 days as our window of interest to align with the timeframe of higher fracture risk observed in the CANVAS trial, and to avoid crossovers that could occur in SGLT-2i exposure with longer periods of follow-up.[1] We kept patients in their initially assigned group for the entire follow-up period, irrespective if they had their initial prescription renewed in follow-up.

We examined hospital encounters for fragility fracture at 365 days and site of fracture as secondary outcomes. To explore possible mechanisms for a short-term higher fracture risk, we also specified hospital encounter with fall, hypotension or severe hypoglycemia as secondary outcomes. These outcomes were evaluated at 180 days as patients can experience them shortly after starting SGLT-2i.[1]

4.2.6 Statistical Analysis

Continuous variables were summarized using mean (standard deviation; SD) or median (25^{th}, 75^{th} percentile) and categorical measures as frequency (proportion). We used inverse probability of treatment weighting on the propensity score to balance comparison groups on baseline health indicators.[38,39] Datasets were complete for all variables except hemoglobin A1c (3,799 values or 2.6% missing, recoded using simple imputation using regression to replace missing values) and urine albumin to creatinine ratio (41,185 values or 28.5% missing, coded as "missing"). Missing values of income quintile were recoded as quintile 3 (389 values or 0.3% missing) and missing values of rurality were recoded as urban area (312 values or 0.2% missing). We used multivariable logistic regression to estimate propensity scores using 71 covariates (see Appendix F) chosen *a priori*; these variables are known to be both associated with antihyperglycemic medication prescribing and fracture risk.[38,39] We weighted patients in the reference group (DPP4i) using average treatment effects for the treated (ATT) weights defined as [propensity score/(1-propensity score)], with patients receiving an SGLT-2i receiving a weight of 1.[39] To avoid instability in our models due to extreme weights, we trimmed weights larger than the 99^{th} percentile, and weights smaller than the 1^{st} percentile. This resulted in a pseudo-sample of patients in the DPP-4i group that had the same distribution of covariates as those in the SGLT-2i group. We compared baseline differences in both the weighted and unweighted group using standardized differences, with ≥10% being considered clinically meaningful.[40]

We then obtained weighted hazard ratios using a weighted Cox proportional hazards regression analysis with the variance and 95% confidence intervals (CI) estimated using bootstrap sampling.[39] A total of 200 bootstrap samples with unrestricted random sampling scheme were drawn from the study samples. Confidence interval widths and p-values were not adjusted for multiple testing.[41] Patients were followed until the development of the outcome of interest, death or end of study follow-up (March 31, 2020).

To assess whether the association between SGLT-2i use and fracture differed by eGFR category, an interaction term was included in our model. We determined whether there was treatment heterogeneity using the overall Wald Chi-square test (not adjusted for multiple testing). We further compared the risk of fracture at 180 days and 365 days

between SGLT-2i and DPP-4i users by eGFR category (eGFR ≥ 90, 60 to < 90, 45 to <60 and 30 to <45 mL/min per 1.73 m^2). We re-weighted within those categories using the propensity scoring method detailed above.[42] All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

4.3 Results

We identified 38,994 new users of SGLT-2i and 105,700 new users of DPP-4i. Details of the cohort build, and number of patients excluded at each step can be found in Appendix G.

Selected unweighted and weighted baseline characteristics for each group can be found in Table 1 (full characteristics in Appendix H). In the unweighted groups, SGLT-2i users were younger (mean age 72 vs 74 years) more likely male (60 vs 53% male), and less likely to have dementia (3 vs 7%) or live in long-term care (1 vs 3%) than new DPP-4i users. There were higher rates of concomitant bisphosphonate use in the DPP-4i group (9 vs 5%). Coronary artery disease was more common in the SGLT-2i users (31 vs 23%), consistent with indications for use. In the unweighted cohort, we also found that a larger proportion of DPP-4i users had lower eGFR levels: 13.1% of DPP-4i users had an eGFR 30 to <45 ml/min/1.73m^2 compared to 6.1% of the SGLT-2i users.

After weighting, baseline characteristics were well balanced between groups except for the proportion of prescriptions written by cardiologists, which remained higher in the SGLT-2i group. When stratified by eGFR, the baseline characteristics of SGLT-2i users and DPP-4i users were well balanced within each eGFR category (see Appendix I).

4.3.1 Prescription Characteristics

Prescription characteristics are provided in Table 2. The mean continuous usage of DPP-4i was slightly longer than SGLT-2i (428 vs 501 days, in SGLT 2i vs DPP 4 respectively). Empagliflozin and sitagliptin were the most prescribed SGLT-2i and DPP-4i, respectively.

4.3.2 Outcomes

After weighting, we observed 342 fractures within 180 days and 689 fractures within 365 days. New SGLT-2i use was not associated with a higher risk of fracture at 180 days compared to new DPP-4i use (weighted HR 0.95, 95% CI: 0.79, 1.13) (Table 3). When examined by fracture site there was also no difference between groups (Appendix J). We found no substantial difference in the 180-day risk of hospital encounter with falls, hypoglycemia, or hypotension (Table 3).

When fracture risk was assessed at 365 days, there was a modestly significant lower risk of fracture in new SGLT-2i users compared to DPP-4i (HR 0.88, 95% CI: 0.77, 1.00).

In subgroup analysis, eGFR did not appear to modify the association between SGLTI-2i versus DDP4i use and fracture outcome at 180 or 365 days (the p-value for interaction: 0.37 and 0.53, respectively) (see Table 4). In all eGFR categories there did not appear to have evidence of a higher risk of fracture with SGLTI-2i versus DDP4i.

4.4 Discussion

Patients with CKD have a 2-5 fold higher risk of fracture compared with the general population.[43,44] Recent guidelines recommend starting SGLT-2i in all patients with diabetic kidney disease and eGFR >30ml/min/1.73m^2 [45], but in short-term studies dapagliflozin and canagliflozin (but not empagliflozin) have been associated with hyperphosphatemia, hyperparathyroidism and increased bone turnover. [8–10,12,46] As such, it is increasingly important to ensure that SGLT-2i do not increase the fracture risk in patients with CKD.

In this large Canadian cohort of older adults, we found that new use of SGLT-2i was not associated with a higher risk of fracture at 180 or 365 days compared to new DPP-4i use. This was also true when results were stratified by eGFR category. This provides further, real world assurance that these medications can be safely prescribed without a higher risk of fracture.

Our results are consistent with a previously published meta-analyses and population-based studies of SGLT-2i vs. placebo or active comparator in the general diabetes populations.[16–23,47] Although the CREDENCE and DAPA-CKD trials of SGLT-2i included patients with CKD, the trials' ability to detect a potential fracture risk was limited by low numbers of events and study of a relatively healthy population.[1,48]

In our study conducted in the real-world (older, higher proportion female), we observed more fracture events than in previous randomized controlled trials but still did not find a higher fracture risk. We did observe a signal of lower risk of fracture in new SGLT-2i users vs. new DPP-4i users in the lowest level of eGFR(30 to <45ml/min/1.73m^2) at 365 days. However, the significance of this finding is limited by small sample size and a lack of adjustment for multiple comparisons. As such, this result may not be reproducible and should be used to generate hypotheses rather than draw conclusions.

While a similar protective effect by eGFR category was seen in one large meta-analysis of SGLT-2i in the general diabetes population (HR for fracture 0.55, 95% CI: 0.37,0.81 vs placebo, the finding did not persist in trials where patients were followed for over 52 weeks [20].

Our study has several strengths. To our knowledge, this is the first study of its kind to specifically examine fracture risk in patients with CKD. We used outpatient lab values which are more accurate in identifying individuals with CKD than administrative data codes which are more sensitive in identifying these patients[49]. We also stratified our analysis based on eGFR categories and were able to achieve well balanced groups within each eGFR strata.

Our cohort was also comprised of individuals prescribed SGLT-2i in usual clinical care, making it more generalizable to real-world older adult population.

However, our study has limitations. To preserve statistical power, we were unable to stratify the analysis by SGLT-2i type. Given that empagliflozin is associated with the least number of metabolic derangements (hyperphosphatemia, hyperparathyroidism) and comprised the most prescriptions, we may have observed a biased result towards a null

effect. Although we adjusted for 71 baseline characteristics and were able to achieve well balanced groups, we cannot rule out residual confounding on unmeasured factors (ie. smoking, severity of diabetes). There were other drugs/factors that we could have included in our analysis (e.g. insulin use, DKA), but we adjusted for a multitude of other measures related to diabetes severity including duration of diabetes, complication rates, care utilization (endocrinologist visits) and number of oral hypoglycemic medications (all were well-balanced between the two groups). Finally, we limited our secondary analyses to one year follow up given the typical duration of continuous use. It is possible that if there is a change in bone density or quality caused by SGLT-2i (such as increased bone turnover and secondary hyperparathyroidism), an associated change in fracture risk may take longer to become apparent.

4.4.1 Conclusions

In this cohort study of over 140,000 patients in Ontario, Canada, new use of SGLT-2i was not associated with a higher risk of fracture compared to new use of DPP-4i. This also held true in patients with an eGFR of 30-90mL/min/1.73m^2. This finding should be re-assuring to clinicians and patients.

Funding Source: This study was supported by the ICES, which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). The research was done at the ICES Western facility with partners which include the Academic Medical Organization of Southwestern Ontario (AMOSO), the Schulich School of Medicine and Dentistry (SSMD), Western University, and the Lawson Health Research Institute (LHRI). Parts of this material are based on data and information compiled and provided by the Canadian Institutes of Health Information (CIHI). The research was conducted by members of the ICES Kidney, Dialysis and Transplantation team, at the ICES Western facility, who are supported by a grant from the Canadian Institutes of Health Research (CIHR). We thank IQVIA Solutions Canada Inc. for use of their Drug Information File. The analyses, conclusions, opinions, and statements expressed herein are solely those of the authors and do not reflect those of the funding or data sources; no endorsement is intended or should be inferred. No endorsement by ICES, the MOHLTC, AMOSO, SSMD, Western University, LHRI, CIHI or CIHR is intended or should be inferred. The

study sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. Dr. Andrea Cowan was supported by Physicians Services Incorporated, LHRI, SSMD and the Division of Nephrology. Dr. Amit Garg was supported by the Dr. Adam Linton Chair in Kidney Health Analytics. Acknowledgements: Parts of this material are based on data and information compiled and provided by the Canadian Institutes of Health Information (CIHI). However, the analyses, conclusions, opinions, and statements expressed herein are those of the author, and not necessarily those of CIHI. CIHI. We thank IQVIA Solutions Canada Inc. for use of their Drug Information File.

Data access/access to data analysis protocol: The analysis was conducted by members of the ICES Kidney Dialysis & Transplantation (KDT) team at the ICES Western facility (London, Ontario). Yuguang Kang was responsible for the data analysis. The protocol can be obtained by emailing Dr. Clemens.

4.5 References

1. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *New England Journal of Medicine*. 2017;377(7):644-657. doi:10.1056/NEJMoa1611925

2. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *New England Journal of Medicine*. 2019;380(4):347-357. doi:10.1056/NEJMoa1812389

3. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *New England Journal of Medicine*. 2015;373(22):2117-2128. doi:10.1056/NEJMoa1504720

4. Lipscombe L, Butalia S, Dasgupta K, et al. Pharmacologic Glycemic Management of Type 2 Diabetes in Adults: 2020 Update. *Canadian Journal of Diabetes*. 2020;44(7):575-591. doi:10.1016/j.jcjd.2020.08.001

5. Food and Drug Administration. HIGHLIGHTS OF PRESCRIBING INFORMATION: Invokana. Published 2018. www.fda.gov/medwatch.

6. Product Monograph: Invokana. Health Canada.

7. Watts NB, Bilezikian JP, Usiskin K, et al. Effects of canagliflozin on fracture risk in patients with type 2 diabetes mellitus. *Journal of Clinical Endocrinology and Metabolism*. 2016;101(1):157-166. doi:10.1210/jc.2015-3167

8. Weir MR, Kline I, Xie J, Edwards R, Usiskin K. Effect of canagliflozin on serum electrolytes in patients with type 2 diabetes in relation to estimated glomerular filtration rate (eGFR). *Current Medical Research and Opinion*. 2014;30(9):1759-1768. doi:10.1185/03007995.2014.919907

9. Kohan DE, Fioretto P, Tang W, List JF. Long-term study of patients with type 2 diabetes and moderate renal impairment shows that dapagliflozin reduces weight

and blood pressure but does not improve glycemic control. *Kidney International*. 2014;85(4):962-971. doi:10.1038/ki.2013.356

10. de Jong MA, Petrykiv SI, Laverman GD, et al. Effects of dapagliflozin on circulating markers of phosphate homeostasis. *Clinical Journal of the American Society of Nephrology*. 2019;14(1):66-73. doi:10.2215/CJN.04530418

11. Blau JE, Taylor SI. Adverse effects of SGLT2 inhibitors on bone health. *Nature Reviews Nephrology*. 2018;14(8):473-474. doi:10.1038/s41581-018-0028-0

12. Bilezikian JP, Watts NB, Usiskin K, et al. Evaluation of bone mineral density and bone biomarkers in patients with type 2 diabetes treated with canagliflozin. *Journal of Clinical Endocrinology and Metabolism*. 2016;101(1):44-51. doi:10.1210/jc.2015-1860

13. Ye Y, Zhao C, Liang J, Yang Y, Yu M, Qu X. Effect of sodium-glucose co-transporter 2 inhibitors on bone metabolism and fracture risk. *Frontiers in Pharmacology*. 2019;9(JAN). doi:10.3389/fphar.2018.01517

14. Ketteler M, Block GA, Evenepoel P, et al. Executive summary of the 2017 KDIGO Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD) Guideline Update: what's changed and why it matters. *Kidney International*. 2017;92(1). doi:10.1016/j.kint.2017.04.006

15. N.B. Watts, C. Roux, D.F. Modlin, J.P. Brown, A. Daniels, S. Jackson, S. Smith, D.J. Zack, L. Zhou, A. Grauer SF. Infections in postmenopausal women with osteoporosis treated with denosumab or placebo : coincidence or causal association ? *Osteoporosis International*. 2012;23:327-337. doi:10.1007/s00198-011-1755-2

16. Schmedt N, Andersohn F, Walker J, Garbe E. Sodium-glucose co-transporter-2 inhibitors and the risk of fractures of the upper or lower limbs in patients with type 2 diabetes: A nested case–control study. *Diabetes, Obesity and Metabolism*. 2019;21(1):52-60. doi:10.1111/dom.13480

17. Fralick M, Kim SC, Schneeweiss S, Kim D, Redelmeier DA, Patorno E. Fracture Risk after Initiating Canagliflozin: a Multi Database Cohort Study. *Annals of Internal Medicine*. 2019;170(3):155-163. doi:10.1016/j.physbeh.2017.03.040

18. Abrahami D, Douros A, Yin H, Yu OHY, Azoulay L. Sodium-glucose cotransporter 2 inhibitors and the risk of fractures among patients with type 2 diabetes. *Diabetes Care*. 2019;42(9):E150-E151. doi:10.2337/dc19-0849

19. Ueda P, Svanström H, Melbye M, et al. Sodium glucose cotransporter 2 inhibitors and risk of serious adverse events: nationwide register based cohort study. *BMJ (Clinical research ed)*. 2018;363:k4365. doi:10.1136/bmj.k4365

20. Cheng L, Li YY, Hu W, et al. Risk of bone fracture associated with sodium–glucose cotransporter-2 inhibitor treatment: A meta-analysis of randomized controlled trials. *Diabetes and Metabolism*. 2019;45(5):436-445. doi:10.1016/j.diabet.2019.01.010

21. Li X, Li T, Cheng Y, et al. Effects of SGLT2 inhibitors on fractures and bone mineral density in type 2 diabetes: An updated meta-analysis. *Diabetes/Metabolism Research and Reviews*. 2019;35(7):1-10. doi:10.1002/dmrr.3170

22. Ruanpeng D, Ungprasert P, Sangtian J, Harindhanavudhi T. Sodium-glucose cotransporter 2 (SGLT2) inhibitors and fracture risk in patients with type 2 diabetes mellitus: A meta-analysis. *Diabetes/Metabolism Research and Reviews*. 2017;33(6). doi:10.1002/dmrr.2903

23. Zhuo M, Hawley CE, Paik JM, et al. Association of Sodium-Glucose Cotransporter-2 Inhibitors with Fracture Risk in Older Adults with Type 2 Diabetes. *JAMA Network Open*. 2021;4(10). doi:10.1001/jamanetworkopen.2021.30762

24. Nitsch D, Mylne A, Roderick PJ, Smeeth L, Hubbard R, Fletcher A. Chronic kidney disease and hip fracture-related mortality in older people in the UK. *Nephrology Dialysis Transplantation*. 2009;24(5):1539-1544. doi:10.1093/ndt/gfn678

25. Ting QC, Haonan L, Huawei Z, Yan PC. Risk of Fractures Associated with Dipeptidyl Peptidase-4 Inhibitor Treatment: A Systematic Review and Meta-

Analysis of Randomized Controlled Trials. *Diabetes Therapy*. 10. doi:10.6084/m9.figshare.8846225

26. Fu J, Zhu J, Hao Y, Guo C, Zhou Z. Dipeptidyl peptidase-4 inhibitors and fracture risk: An updated meta-analysis of randomized clinical trials. *Scientific Reports*. 2016;6. doi:10.1038/srep29104

27. Finance OM of. Ontario Population Projections, 2018–2046. Queen's Printer for Ontario. Published 2019. Accessed February 12, 2020. https://www.fin.gov.on.ca/en/economy/demographics/projections/#s3b

28. Langan SM, Schmidt SA, Wing K, et al. The reporting of studies conducted using observational routinely collected health data statement for pharmacoepidemiology (RECORD-PE). *BMJ (Clinical research ed)*. 2018;363:k3532. doi:10.1136/bmj.k3532

29. Ontario Drug Benefit Formulary. Search Results. Accessed April 3, 2019. https://www.formulary.health.gov.on.ca/formulary/results.xhtml?q=flozin&type=1

30. Levey AS, Stevens LA. Estimating GFR Using the CKD Epidemiology Collaboration (CKD-EPI) Creatinine Equation: More Accurate GFR Estimates, Lower CKD Prevalence Estimates, and Better Risk Predictions. *American Journal of Kidney Diseases*. 2010;55(4):622-627. doi:10.1053/j.ajkd.2010.02.337

31. CKD & Drug Dosing: Information for Providers. NIDKK. Published 2015. Accessed July 8, 2021. https://www.niddk.nih.gov/health-information/professionals/advanced-search/ckd-drug-dosing-providers?dkrd=hisce0131

32. Garg AX, Mamdani M, Juurlink DN, van Walraven C. Identifying individuals with a reduced GFR using ambulatory laboratory database surveillance. *Journal of the American Society of Nephrology*. 2005;16(5):1433-1439. doi:10.1681/ASN.2004080697

33. Inal B, Oguz O, Emre T, et al. Evaluation of MDRD, Cockcroft-Gault, and CKD-EPI Formulas in the Estimated Glomerular Filtration Rate. *Clinical Laboratory*. 2014;60(10/2014). doi:10.7754/Clin.Lab.2014.131110

34. Brimble KS, Treleaven D, Cooper R, Blake PG. Removal of eGFR Adjustment for Race in Ontario | CMAJ. Canadian Medical Association Journal. Published 2021. Accessed July 20, 2021. https://www.cmaj.ca/content/removal-egfr-adjustment-race-ontario

35. Iksander C, Cherney DZ, Clemens KK, et al. Use of sodium–glucose cotransporter-2 inhibitors and risk of acute kidney injury in older adults with diabetes: a population-based cohort study. *Canadian Medical Association Journal*. Published online April 12, 2020:E351-E360.

36. O'Donnell S. Use of administrative data for national surveillance of osteoporosis and related fractures in Canada: Results from a feasibility study. *Archives of Osteoporosis*. 2013;8(1-2). doi:10.1007/s11657-013-0143-2

37. Papaioannou A, Kennedy CC, Ioannidis G, et al. Comparative trends in incident fracture rates for all long-term care and community-dwelling seniors in Ontario, Canada, 2002–2012. *Osteoporosis International*. 2016;27(3):887-897. doi:10.1007/s00198-015-3477-3

38. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behavioral Research*. 2011;46(3):399-424. doi:10.1080/00273171.2011.568786

39. Austin PC. Variance estimation when using inverse probability of treatment weighting (IPTW) with survival analysis. *Statistics in Medicine*. 2016;35(30):5642-5655. doi:10.1002/sim.7084

40. Austin PC. Using the Standardized Difference to Compare the Prevalence of a Binary Variable Between Two Groups in Observational Research. *Communications*

in Statistics - Simulation and Computation. 2009;38(6):1228-1234. doi:10.1080/03610910902859574

41. Harrington D, D'Agostino RB, Gatsonis C, et al. New Guidelines for Statistical Reporting in the Journal . *New England Journal of Medicine*. 2019;381(3):285-286. doi:10.1056/nejme1906559

42. Izem R, Liao J, Hu M, et al. Comparison of propensity score methods for pre-specified subgroup analysis with survival data. *Journal of Biopharmaceutical Statistics*. 2020;30(4):734-751. doi:10.1080/10543406.2020.1730868

43. Dooley AC, Weiss NS, Kestenbaum B. Increased Risk of Hip Fracture Among Men With CKD. *American Journal of Kidney Diseases*. 2008;51(1):38-44. doi:10.1053/j.ajkd.2007.08.019

44. Naylor KL, McArthur E, Leslie WD, et al. The three-year incidence of fracture in chronic kidney disease. *Kidney International*. 2014;86(4):810-818. doi:10.1038/ki.2013.547

45. KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. *Kidney International*. 2020;98(4):S1-S115. doi:10.1016/j.kint.2020.06.019

46. Kohler S, Zeller C, Iliev H, Kaspers S. Safety and Tolerability of Empagliflozin in Patients with Type 2 Diabetes: Pooled Analysis of Phase I–III Clinical Trials. *Advances in Therapy*. 2017;34(7):1707-1726. doi:10.1007/s12325-017-0573-0

47. Qian BB, Chen Q, Li L, Yan CF. Association between combined treatment with SGLT2 inhibitors and metformin for type 2 diabetes mellitus on fracture risk: a meta-analysis of randomized controlled trials. *Osteoporosis International*. 2020;31(12):2313-2320. doi:10.1007/s00198-020-05590-y

48. Heerspink HJL, Stefánsson B v., Correa-Rotter R, et al. Dapagliflozin in Patients with Chronic Kidney Disease. *New England Journal of Medicine*. 2020;383:1436-1446. doi:10.1056/nejmoa2024816

49. Fleet JL, Dixon SN, Shariff SZ, et al. Detecting chronic kidney disease in population-based administrative databases using an algorithm of hospital encounter and physician claim codes. *BMC Nephrology*. 2013;14(1). doi:10.1186/1471-2369-14-81

Table 4.1- Selected characteristics of older adults in Ontario, Canada, upon initiation of an SGLT-2i or DPP-4i

	Unweighted (N=144,694)			Weighted (N=76,443)		
	DPP-4i users (N=105,700)	SGLT-2i users (N=38,994)	Standardized Difference	DPP4i users (N=37,449)	SGLT2i users (N=38,994)	Standardized Difference
Demographics						
Age, mean, y (SD)	74 (7)	72 (5)	0.38	72 (3)	72 (5)	0.00
Female No. (%)	49,289 (47)	15,457 (40)	0.14	15,258 (41)	15,457 (40)	0.02
Long Term Care No. (%)	3,560 (3)	283 (1)	0.19	302 (1)	283 (1)	0.01
Prescriber Specialty, No. (%)						
Cardiology	440 (0)	1,580 (4)	0.25	636 (2)	1,580 (4)	0.14
Endocrinology	8,743 (8)	5,480 (14)	0.18	5,068 (14)	5,480 (14)	0.02
General Practitioner	85,858 (81)	26,190 (67)	0.32	26,398 (71)	26,190 (67)	0.07
Internal Medicine	3,579 (3)	2,652 (7)	0.16	2,421 (7)	2,652 (7)	0.01
Nephrology	803 (1)	758 (2)	0.10	612 (2)	758 (2)	0.02
Other	6,277 (6)	2,334 (6)	0.00	2,313 (6)	2,334 (6)	0.01
Comorbidities, No.(%)						
Mean duration of diabetes, y (SD)	11.5 (7.4)	12.4 (7.6)	0.11	12.2 (4.4)	12.4 (7.6)	0.03
Fragility fracture	4,012 (4)	1,204 (3)	0.04	1,197 (3)	1,204 (3)	0.01
Previous fall	17,225 (16)	5,572 (14)	0.06	5,439 (15)	5,572 (14)	0.01
Dementia	7,636 (7)	1,094 (3)	0.20	1,111 (3)	1,094 (3)	0.01
Rheumatoid arthritis	2,398 (2)	848 (2)	0.01	815 (2)	848 (2)	0.00
Osteoporosis	7,839 (7)	1,969 (5)	0.10	1,926 (5)	1,969 (5)	0.00
Coronary artery disease	24,571 (23)	12,258 (31)	0.18	10,961 (29)	12,258 (31)	0.05
Diabetic retinopathy	750 (1)	338 (1)	0.02	314 (1)	338 (1)	0.01
Diabetic neuropathy	1,431 (1)	604 (2)	0.01	577 (2)	604 (2)	0.00

Medication Use, No. (%)						
Bisphosphonates	9,199 (9)	1,952 (5)	0.15	1,939 (5)	1,952 (5)	0.01
Denosumab	2,053 (2)	486 (1)	0.06	479 (1)	486 (1)	0.01
Oral steroid	8,038 (8)	2,732 (7)	0.02	2,641 (7)	2,732 (7)	0.00
Diabetes and Kidney Function, No. (%)						
Number of diabetes medications						
0	37,006 (35)	10,916 (28)	0.15	10,454 (28)	10,916 (28)	0.00
1	51,484 (49)	20,902 (54)	0.10	19,976 (53)	20,902 (54)	0.01
2+	17,210 (16)	7,176 (18)	0.06	7,019 (19)	7,176 (18)	0.01
Metformin	61,485 (58)	25,896 (66)	0.17	24,803 (66)	25,896 (66)	0.00
Mean Hemoglobin A1C,% (SD)	8.1 (1.6)	8.0 (1.5)	0.03	8.1 (0.9)	8.0 (1.5)	0.02
Diabetes management	54,022 (51)	22,108 (57)	0.11	21,383 (57)	22,108 (57)	0.01
Mean number of GP visits (SD)	14.2 (19.2)	12.37 (15.0)	0.11	12.4 (8.2)	12.37 (14.96)	0.01
Mean number of Endocrinology visits (SD)	0.5 (2.0)	0.8 (2.2)	0.13	0.7 (1.2)	0.8 (2.2)	0.06
Mean eGFR, ml/min/1.73m^2 (SD)	69 (19)	73 (17)	0.23	73 (10)	73 (17)	0.01
eGFR category (ml/min/1.73m^2)						
≥90	14,853 (14)	6,485 (17)	0.07	6,319 (17)	6,485 (17)	0.01
60-<90	55,500 (53)	23,520 (60)	0.16	22,547 (60)	23,520 (60)	0.00
45-<60	20,617 (20)	6,577 (17)	0.07	6,250 (17)	6,577 (17)	0.01
30-<45	14,730 (14)	2,412 (6)	0.26	2,332 (6)	2,412 (6)	0.00

Abbreviations: DPP-4i, dipeptidyl peptidase 4 inhibitor; SGLT-2i, sodium glucose cotransporter 2 inhibitor; eGFR- estimated glomerular filtration rate measured in ml/min/1.73m^2; SD- standard deviation

The most recent eGFR measurement in the 365-day period before the cohort entry date (including the cohort entry date); eGFR was calculated using the Chronic Kidney Disease (CKD)–Epidemiology (EPI) equation: $141 \times \min([\text{serum creatinine concentration in } \mu\text{mol/L}/88.4]/\kappa, 1)^{\alpha} \times \max([\text{serum creatinine concentration in } \mu\text{mol/L}/88.4]/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018$ [if female] κ=0.7 if female and 0.9 if male; α=-0.329 if female and -0.411 if male; min=the minimum of serum creatinine concentration/κ or 1; max=the maximum of serum creatinine concentration/κ or 1. Based on recent Ontario Renal Network guidelines, race was not factored into the calculation of eGFR.

Table 4.2- Prescription Characteristics of SGLT-2i and DPP-4i

Medication		Mean Continuous Use, days (SD)	Median Continuous Use, days (IQR)
SGLT-2i	All (N=38,994)	428 (414)	287(89-645)
	Empagliflozin (n=22,095)	379 (342)	283(85-566)
	Canagliflozin (n=11,939)	464 (477)	272(78-711)
	Dapagliflozin (n=4,960)	414 (368)	291(91-664)
DPP-4i	All (N=105,700)	501 (454)	348(135-778)
	Sitagliptin (n=78,633)	480 (443)	329(125-733)
	Linagliptin (n=22,415)	504 (452)	358(125-794)
	Saxagliptin (n=4,652)	470 (462)	283(104-723)

Abbreviations: DPP-4i, dipeptidyl peptidase 4 inhibitor; SGLT-2i, sodium glucose cotransporter 2 inhibitor SD: Standard deviation; IQR: interquartile range

Table 4.3- Primary and secondary outcomes in the SGLT-2i and DPP4i cohorts

Outcome (at 180 days)	DPP-4i (N=37,449) n (%)	SGLT-2i (N=38,994) n (%)	wHR (95% CI)
All Fracture	172 (0.5%)	170 (0.4%)	0.95 (0.79-1.13)
Falls	880 (2.4%)	897 (2.3%)	0.98 (0.91-1.05)
Hypotension	40 (0.1%)	41 (0.1%)	0.98 (0.65-1.47)
Hypoglycemia	81 (0.2%)	77 (0.2%)	0.91 (0.68-1.22)

Abbreviations: DPP-4i, dipeptidyl peptidase 4 inhibitor; SGLT-2i, sodium glucose cotransporter 2 inhibitor wHR: weighted hazard ratio, CI: Confidence interval

Table 4.4- Fractures at 180 and 365 days assessed by eGFR group

eGFR Group (ml/min/1.73m^2)	Medication	Fracture at 180 days N (%)	wHR (95% CI)	p-value for subgroup interaction	Fracture at 365 days N (%)	wHR (95% CI)	p-value for subgroup interaction
All	DPP4i N=37,449	172 (0.46%)	0.95 (0.79-1.13)	N/A	360 (0.96%)	0.88 (0.77-1.00)	N/A
	SGLT-2i N=38,994	170 (0.44%)			329 (0.84%)		
eGFR ≥90	DPP4i N=6,330	28 (0.45%)	0.79 (0.46-1.38)	0.37	61 (0.96%)	0.90 (0.63-1.28)	0.53
	SGLT-2i N=6,485	23 (0.35%)			56 (0.86%)		
eGFR 60 to < 90	DPP4i N=22,625	95 (0.42%)	1.1(0.81-1.36)		194 (0.86%)	0.94 (0.78-1.13)	
	SGLT-2i N=23,520	104 (0.44%)			189 (0.80%)		
eGFR 45 to < 60	DPP4i N=6,198	28 (0.46%)	1.0(0.70-1.50)		68 (1.10%)	0.82 (0.61-1.10)	
	SGLT-2i N=6,577	31 (0.47%)			59 (0.90%)		
eGFR 30 to < 45	DPP4i N=2,206	19 (0.88%)	0.56 (0.30-1.06)		36 (1.64%)	0.64 (0.43-0.95)	
	SGLT-2i N=2,412	12 (0.50%)			25 (1.04%)		

Abbreviations: DPP4i, dipeptidyl peptidase 4 inhibitor; SGLT-2i, sodium glucose cotransporter 2 inhibitor, eGFR: estimated glomerular filtration rate, wHR: weighted hazard ratio, CI: confidence interval

Chapter 5

5 Hypocalcemia risk of denosumab across the spectrum of kidney disease: A population-based cohort study

Andrea Cowan[1,2]*, Nivethika Jeyakumar[1,3], Eric McArthur[1,3], Jamie L Fleet [3,4,5,7], Tharsan Kanagalingam[5], Igor Karp[6], Tayyab Khan[2,7], Flory Tsobo Muanda[1], Danielle M Nash[1,3,6], Samuel A Silver[1,8], Jenny Thain[2,7], Matthew A Weir[1,2,3], Amit X Garg[1,2,3,5,6,], Kristin K Clemens [1,2,3,5,6,7]

1. ICES, ON, Canada
2. Department of Medicine, Western University, London ON, Canada
3. Lawson Health Research Institute, London Health Sciences Centre, London ON, Canada
4. Department of Physical Medicine and Rehabilitation, Western University, London, ON, Canada
5. Schulich School of Medicine and Dentistry, Western University, London, ON, Canada
6. Department of Epidemiology & Biostatistics, Western University, London ON, Canada
7. St. Joseph's Health Care London, London ON, Canada
8. Queen's University, Kingston, Ontario, Canada

5.1 Introduction

Patients with chronic kidney disease (CKD) are at increased risk of skeletal fracture due to the presence of CKD-mineral and bone disorder, underlying osteoporosis, functional impairment, and substantial comorbidities.[1] Those receiving maintenance dialysis have a 5-fold higher risk of fracture compared to the general population, and even women with relatively mild CKD (estimated glomerular filtration rate [eGFR] 30-45ml/min/1.73m^2), have double the fracture risk of women with an eGFR ≥60ml/min/1.73m^2.[2–4] Moreover, patients across the CKD spectrum who suffer a fracture are at high risk of complications, including death and loss of function. [53,5–9 8]

Denosumab is a commonly used antiresorptive agent which treats osteoporosis by reducing osteoclast activity through inhibiting the Receptor Activator of Nuclear Factor Kappa-β Ligand (RANKL). [10,11] Because pharmacokinetic studies have shown no drug accumulation across levels of kidney function, it is approved for use in all stages of CKD.[12,13] Although there have been no devoted studies of the effect of denosumab on fracture risk in patients with CKD, a secondary analysis of the FREEDOM trial showed that denosumab was relatively safe and effective in preventing fracture across eGFR strata. However this included only 73 patients with an eGFR <30 ml/min/1.73m^2 and none with an eGFR <15ml/min/1.73m^2 or receiving dialysis. [13,14]

Missing from large clinical trials of denosumab, has been a thorough assessment of hypocalcemia risk after administration.[15,16] When denosumab has been used in real-world populations, an increased risk of hypocalcemia has been observed, particularly in those with CKD.[10,11,17,18] In some cases, hypocalcemia resulted in severe weakness, tetany and prolonged QT requiring admission to hospital. The reported incidence of hypocalcemia has varied depending on the definition used, prophylaxis provided, and population studied, but estimates range from 15 to 60%.[13,19–23] While lower kidney function has consistently been identified as a risk factor for hypocalcemia, information on other predictors is poor.

In a large cohort of patients from Canada's most populous province, we sought to determine the real-world incidence of hypocalcemia with the use of denosumab across the spectrum of kidney function. We used oral bisphosphonate as a comparator as the risk of hypocalcemia with this therapy is minimal.[24] We also aimed to understand risk factors for denosumab-induced hypocalcemia across the spectrum of kidney disease.

5.2 Methods

5.2.1 Design and Setting

We conducted a population-based, retrospective cohort study of residents of Ontario, Canada from 2012 to 2020 using administrative health data at ICES (formerly known as the Institute for Clinical Evaluative Sciences). In Ontario, residents have universal access to health care, and those aged 65 years and older have access to outpatient prescription

drug coverage which is captured in ICES databases. In 2020, Ontario's population was 14.7 million, 2.4 million of which were over 65.[25] Losses to follow up occur only with emigration from the province, estimated to occur at a rate of less than 0.2% per year.[26]

The use of data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act which does not require review by the Research Ethics Board. We have reported this study according to recommended guidelines for the Reporting of studies Conducted using Observational Routinely collected health Data for PharmacoEpidemiology (RECORD-PE; Supplementary Material A).[27]

5.2.2 Data Sources

Patient characteristics, prescription drug use, covariate information and outcome data were obtained from eight administrative health databases. Datasets are linked using encoded identifiers and analyzed at ICES. The data sets included Canadian Institute for Health Information's Discharge Abstract Database [CIHI-DAD] and National Ambulatory Care Reporting System [CIHI-NACRS] Database.

Administrative codes are entered into CIHI-DAD and NACRS by trained personnel in Ontario hospitals based on CIHI guidelines. Coders review medical charts to assign diagnoses and procedures using the International Classification of Diseases-10 (ICD-10) codes. These personnel only assign codes based upon physician-recorded diagnoses and do not interpret other medical tests or results. Prescribed medications were identified using the Ontario Drug Database (ODB). Records of osteoporosis medications dispensed through ODB have excellent agreement with self-reported use of these therapies.[28] Additional databases used are outlined in Supplementary Material B.

5.2.3 Patients

All Ontario residents who had a new prescription for denosumab (60 mg subcutaneous dose) or an oral bisphosphonate (etidronate, alendronate, and risedronate were used as they are on the provincial drug formulary) between February 2012 and September 2020 were considered for inclusion. Drug identification numbers used to identify denosumab and bisphosphonate prescriptions are listed in Supplementary Material C.

Bisphosphonates were chosen as an active comparator in order to descriptively compare calcium levels in those with osteoporosis, but not treated with denosumab. We do acknowledge that bisphosphonates are not recommended for use in those with advanced kidney disease.

After standard data cleaning (invalid or missing ICES key number, missing date of birth, age or sex, non-Ontario resident; death on or before index prescription date), we excluded the following patients: <66 years of age (to allow a full 1 year of lookback for baseline medication use); evidence of concurrent denosumab and bisphosphonate prescriptions (where active use was defined as 1.5 times the length of the dispensed prescription); evidence of use of the same drug class in the 5 years prior (to ensure new users, a longer look-back was used as bisphosphonates can accumulate in bone and affect bone density for years after stopping); [29] evidence of emergency department visit or hospital discharge in the two days prior to the new prescription (to ensure medication was newly prescribed on an outpatient basis) and residents who lived in the catchment area of a hospital that did not contribute laboratory values to OLIS (to ensure all follow-up calcium tests performed in hospital would be available). We also excluded individuals with unknown renal function (i.e. no evidence of chronic dialysis or a serum creatinine measurement in the 1 year prior).

If patients had evidence of both an eligible new bisphosphonate and denosumab prescription over the accrual period, we preferentially included them in the denosumab cohort as this was the primary cohort of interest.

5.2.4 Baseline Characteristics

We captured the baseline characteristics of new denosumab and bisphosphonate users including their demographics, comorbidities in the preceding five years, health care utilization in the prior year, baseline laboratory testing in the prior year and prescriptions filled in the preceding four months (unless otherwise indicated: historical bisphosphonate and denosumab use was captured in the preceding one year.) Codes used to capture baseline characteristics are presented in Supplementary Material D.

We determined kidney function based on the most recent serum creatinine measurement or evidence of chronic dialysis in the year prior to their new prescription (the index date). Outpatient serum creatinine values measured on a single occasion in our region are usually in a steady state and represent a patient's chronic level of kidney function.[30] We used serum creatinine values to calculate the eGFR using the Chronic Kidney Disease Epidemiology (CKD-EPI) equation without race.[31] Individuals receiving maintenance dialysis were identified using administrative codes for hemodialysis or peritoneal dialysis (see Supplementary Material D). Patients were categorized in the following baseline kidney function groups: eGFR ≥60 ml/min/1.73m^2, eGFR 45 to <60 ml/min/1.73m^2, eGFR 30 to <45 ml/min/1.73m^2, eGFR 15 to <30ml/min/1.73m^2 and eGFR <15 ml/min/1.73m^2 or receipt of chronic dialysis.

We determined continuous use of bisphosphonates and denosumab by identifying consecutive prescription claims for the same medication within a period equivalent to 1.5 times the number of days supplied for the previous prescription. For denosumab users, a single dose was assumed to be a 6-month prescription.

5.2.5 Outcomes

Our primary outcome was mild hypocalcemia within 180 days of the new denosumab or bisphosphonate prescription. We defined mild hypocalcemia as an albumin-corrected serum calcium <2.0 mmol/L or ionized calcium <1.0 mmol/L, in line with the Common Terminology for Adverse Events version 5.0.[32] We chose 180 days as it allowed us to capture a period when the risk of hypocalcemia is thought to be highest (~4 weeks following injection) and to account for potential delays between drug dispensing and administration.[20]

Secondary outcomes included severe hypocalcemia (corrected serum calcium <1.8 mmol/L or ionized calcium <0.9 mmol/L) within 180 days of denosumab dispensing. We also determined the time to first calcium test and time to hypocalcemia. Patients were followed until evidence of the outcome of interest, death, or completion of follow-up (180 days).

5.2.6 Statistical Analysis

Baseline characteristics for both new denosumab and bisphosphonate users were summarized using descriptive statistics. Continuous measures were expressed as means (standard deviation) or medians (25^{th}, 75^{th} percentile), and categorical measures were expressed as frequency (proportion). The 180-day cumulative incidence of hypocalemia was generated from cumulative incidence functions directly, accounting for time to event and censoring. Results for all outcomes were reported separately for denosumab and bisphosphonate users and by kidney function category (eGFR ≥ 60, eGFR 30 to < 60, eGFR 15 to < 30 and eGFR <15 or receipt of maintenance dialysis). A previous study in Ontario showed a substantial differences between the characteristics of those newly prescribed denosumab and bisphosphonates (those newly prescribed denosumab are typically older, more often resided in long term care and had more comorbidities including advanced kidney disease).[33] Given our primary aim was to provide "bedside estimates" of hypocalcemia risk, we decided *a priori* not to attempt to balance baseline characteristics

Risk factors for mild hypocalcemia were assessed using Cox proportional hazards regression, with candidate predictors selected based upon literature review and data availability. In the case of missing data for continuous predictors, the predictor was divided into categories, including a missing category. We planned *a priori* for the creation of two models; one for the entire cohort of new denosumab users, and one for those with an eGFR <30 ml/min/1.73 m^2. In the general denosumab cohort, we included age, sex, eGFR, calcitriol use, previous bisphosphonate use, baseline calcium, baseline parathyroid hormone (PTH) (divided by tertile) and baseline 25-hydroxyvitamin D (divided into ≥ and <75nmol/L). In those with an eGFR <30 ml/min/1.73m2, we elected to restrict to those with a baseline calcium measurement available as we anticipated this to be a strong predictor, and per guidelines, should be measured prior to denosumab administration.[34] In this model, we also included age, sex, eGFR, calcitriol use, previous bisphosphonate use, baseline calcium and baseline parathyroid hormone (PTH) (divided by tertile). Vitamin D was not included in the low eGFR group as we anticipated (and observed) a large degree of missing data. When developing the prediction models, the proportional hazards

assumption was assessed using Schoenfeld residuals. Model performance was assessed using the optimism-corrected c-index. We performed all analysis using SAS version 9.4 (SAS Institute, Cary, NC).

5.3 Results

We identified 59,151 patients newly prescribed denosumab, and 56,847 patients newly prescribed bisphosphonates over the study period (Supplementary Material E).

Table 1 shows selected baseline characteristics for new users of denosumab and bisphosphonates. As expected, new users of denosumab were older, more often had dementia, and more often lived in long-term care than new users of bisphosphonates. A higher proportion also had a history of fragility fracture compared to those newly prescribed bisphosphonates. Approximately one-third of those prescribed denosumab had a baseline calcium measured within the prior year, and only 38% had a baseline 25-hyroxyvitamin D measured.

The baseline characteristics of new users of both medications stratified by kidney function category are presented in Supplementary Material F and G. In general, we found that those with a lower (vs higher) eGFR were older and had more comorbidities including coronary artery disease and diabetes across both drug groups. As eGFR declined, the proportion of new denosumab users who had a baseline calcium measured increased (74% of those with an eGFR <15 ml/min/1.73m^2 or receiving maintenance dialysis), while the proportion of those with a 25-hydroxyvitamin D level checked decreased (30% of those in the eGFR <15 ml/min/1.73m^2 or maintenance dialysis group had a baseline level checked).

5.3.1 Characteristics of new prescriptions

The characteristics of new prescriptions for denosumab and bisphosphonates are presented in Supplementary Material H. The median (25th, 75th percentile) duration of use of denosumab was 456 days (100, 933) versus 218 days (45, 624) for bisphosphonates. One year after the new prescription, more than half (57%) of bisphosphonate users stopped taking the drug, compared with 33% of denosumab users. We also found that

new prescriptions for both therapies were most often provided by primary care physicians, even in those with advanced kidney disease (72% of denosumab prescriptions and 66% of bisphosphonate prescriptions with an eGFR <15ml/min/1.73m^2).

5.3.2 Incidence of Laboratory Documented Hypocalcemia

In new users of denosumab, 33% had a calcium value measured within 180 days of the denosumab prescription (median time to test [25th, 75th percentile] 53 days [22, 98]). In new bisphosphonate users, 22% had a calcium value drawn within 180 days, with a median time to test (25th, 75th percentile) of 83 days (33, 132). As kidney function worsened, the proportion of individuals with a calcium tested after administration increased (Table 2).

The incidence of mild hypocalcemia (albumin corrected serum calcium <2.00mmol/L or ionized calcium < 1.00 mmol/L) within 180 days of filling both medications is shown in Table 2. Overall, the cumulative incidence of hypocalcemia after a new prescription for denosumab was 0.6% (95% CI 0.6, 0.7%) compared with 0.3% [95% CI 0.3, 0.3] in bisphosphonate users. The 180-day incidence of severe hypocalcemia was 0.2% (95% CI 0.2, 0.3) in new denosumab users vs 0.1% (95% CI 0.1, 0.1) in new bisphosphonate users.

In denosumab users, the incidence of hypocalcemia increased as kidney function declined. In those with an eGFR 15 to <30ml/min/1.73m^2 for example, the incidence was 3.5% (95% CI 2.7, 4.4), compared with 24.1% (95% CI 18.1, 30.7) in the eGFR < 15 ml/min/1.73m^2 group. Those in the lowest kidney function category also had the highest incidence of severe hypocalcemia (albumin corrected calcium <1.8mmol/L or ionized <0.9mmol/L) at 180 days (14.9% [95% CI 10.1, 20.7]).

5.3.3 Prediction Model

There was a high degree of missing baseline laboratory values (e.g.71%, 83% and 62% of denosumab users were missing a baseline calcium, parathyroid hormone and vitamin D value respectively). In both the overall denosumab cohort and in those with an eGFR <30 ml/min/1.72m^2, a higher baseline eGFR, higher baseline calcium, and older age, were

associated with a lower risk of recorded hypocalcemia. In those with an eGFR <30 ml/min/1.73m2, there was a 10% reduction in the risk of recorded hypocalcemia for every 1ml/min/1.73m^2 increase in eGFR and a 27% lower risk of hypocalcemia for every 0.1mmol/L increase in calcium (Table 3). The models for the entire cohort and the eGFR <30ml/min/1.73m^2 cohort had a c-index of 0.73 and 0.78, respectively, suggesting moderate discrimination.

5.4 Discussion

In this large, population-based cohort study, we identified over 59,000 patients newly prescribed denosumab and found that the overall rate of recorded mild hypocalcemia (<2 mmol/L) was low, although quantitatively higher in those prescribed oral bisphosphonates. We do expect that had we used intravenous bisphosphonates, the hypocalcemia risk would have been higher, but access to IV bisphosphoantes is limited in Ontario.[35–37] The incidence of recorded hypocalcemia in new users of denosmab increased substantially with lower levels of kidney function, with approximately one quarter of those with an eGFR<15ml/min/1.73m^2 experiencing hypocalcemia and 15% having a level below 1.8mmol/L. This risk is similar to those taking cinacalcet (18% incidence of calcium <1.87mmol/L), or who receive a parathyroidectomy for secondary hyperparathyroidism (31% incidence of calcium <1.87mmol/L), both of which are strategies used to decrease fracture risk in individuals receiving dialysis.[38–41]

To our knowledge, this is the largest cohort study of new denosumab users focused upon the risk of hypocalcemia following drug administration. Denosumab use has been increasing over the last 10 years, including in populations not studied in the original efficacy trials (ie. those with CKD).[42–44] As a result, studies of real world use have become increasingly important to identify and quantify previously undescribed side effects.[15,16] Our results are consistent with the incidence of hypocalcemia observed in smaller cohort studies of patients with stages 4, 5 and 5D CKD (See Supplementary Material J for a summary of literature). However, the majority of these studies had protocolized calcium monitoring for the first month after injection, compared to our study where only one third of individuals had their calcium checked within 180 days of receiving denosumab.[8] The small proportion of individuals who had a calcium checked in

our study is likely due to a lack of guidance in common osteoporosis guidelines. Canadian and American guidelines recommend checking and repleting calcium and vitamin D prior to denosumab initiation but give no guidance around post-denosumab monitoring.[45,46] Conversely, guidelines from international organizations and the United Kingdom, recommend checking calcium levels two weeks after initiation of denosumab in those with risk factors such as CKD.[47,48] In this study, we could not capture calcium and vitamin D supplements, and some patients in routine care may not have been receiving supplemental calcium and vitamin D in advance of denosumab. As a result, some hypocalcemia may be mitigated by careful patient screening and supplementation prior to denosumab initiation. Of note, in our study very few patients had a calcium and 25 hydroxyvitamin D level checked in advance of denosumab (only 29% and 38% of individuals respectively in the overall cohort). As kidney function declined, the frequency of calcium monitoring increased, and vitamin D monitoring decreased: in those with an eGFR <30ml/min/1.73m^2 calcium and vitamin D were measured in 54% and 35% respectively. This emphasizes the importance of education for prescribers in this area, particularly for general practitioners who prescribe the majority of new denosumab prescriptions.

Lower baseline eGFR and concentration of serum calcium were two important predictors for a higher risk of hypocalcemia after denosumab use. This was consistent with previous evidence in the general population, which included very few individuals with advanced kidney disease.[34,49]

Contrary to expectation, older age was found to be associated with a decreased incidence of hypocalcemia perhaps because physicians have a higher index of suspicion for hypocalcemia in older individuals and are more likely to prescribe prophylaxis. Although were only included individuals over 65 years old, we expect hypocalcemia risks would be similar in those under 65. Our prediction tool performed with reasonable accuracy and could be clinically important in identifying individuals who might be at risk of this outcome as well as those who could benefit from vitamin D and calcium prophylaxis and more rigorous monitoring.

5.4.1 Strengths and Limitations

We assembled a very large cohort of over 59,000 patients newly initiated on denosumab and examined the risk of hypocalcemia in a routine care setting, resulting in widely generalizable results. We also included over 2000 individuals with an eGFR <30 ml/min/1.73m^2, a population typically underrepresented in standard clinical trials.

Given the small numbers in the low eGFR groups and the significant differences in the baseline characteristics between new denosumab and bisphosphonate users, we chose not to undertake any matching or weighting to balance the groups. Thus, the incidence of hypocalcemia cannot be directly compared across. For example, more patients prescribed denosumab vs. a bisphosphonate had a lower eGFR and were more comorbid which may independently influenced their risk of hypocalcemia.

In order to ensure we were able to capture all measured hypocalcemia, we excluded patients who did not reside within a hospital catchment area with linked laboratory data (approximately 39% of the Ontario population.) This led to the loss of ~ 142,000 patients with eligible prescriptions. However, we do not expect those individuals to differ from our included population, nor between denosumab and bisphosphonate groups. [50] We likely did not capture all cases of hypocalcemia in our cohort because approximately two-thirds of new denosumab users did not have calcium monitored afterward. However, in the highest risk groups (eGFR <15ml/min/1.73m^2) over 90% had a calcium level checked and those who develop symptoms of hypocalcemia are likely to have had a level measured. Similarly, the prediction modeling, was limited by a large amount of missing data for PTH and 25 hydroxyvitamin D and must only be considered exploratory. There was some evidence for nonproportionality of eGFR in model 1 and calcitriol in model 2. However in the interests of creating an easy to interpret and clinically useful model, we chose not to explore these covariates as time varying. Although we were able to measure prescriptions for activated vitamin D use, we could not capture over-the-counter calcium and Vitamin D3 use, so we cannot tell if patients received prophylaxis against hypocalcemia..

In conclusion, in a large cohort of real-world new users of denosumab, rates of hypocalcemia were overall low, though increased with advanced kidney disease. Our study suggests the importance of further education, careful patient selection for denosumab and pro and post denosumab calcium monitoring. More information on the efficacy of denosumab in patients with lower levels of kidney function is also needed, along with how to best mitigate the risk of hypocalcemia in this patient population.

Funding: This study was supported by the ICES, which is funded by an annual grant from the Ontario Ministry of Health (MOH) and the Ministry of Long-Term Care (MLTC). The research was done at the ICES Western facility with partners which include the Academic Medical Organization of Southwestern Ontario (AMOSO), the Schulich School of Medicine and Dentistry (SSMD), Western University, and the Lawson Health Research Institute (LHRI). Parts of the analysis were supported by the Opportunities Fund of the Academic Health Sciences Centre Alternative Funding Plan of the Academic Medical Organization of Southwestern Ontario (AMOSO) and a Project Grant from the Canadian Institutes of Health Research (CIHR). Parts of this material are based on data and information compiled and provided by the Ministry of Health (MOH) and Canadian Institutes of Health Information (CIHI). However, the analyses, conclusions, opinions, and statements expressed herein are solely those of the authors, and do not reflect those of the funding or data sources; no endorsement is intended or should be inferred. The research was conducted by members of the ICES Kidney, Dialysis and Transplantation team, at the ICES Western facility, who are supported by a grant from the Canadian Institutes of Health Research (CIHR). We thank IQVIA Solutions Canada Inc. for use of their Drug Information File. Dr. Andrea Cowan was supported by Physicians Services Incorporated, LHRI, SSMD, the University of Western Department of Medicine and the Division of Nephrology. Dr. Amit X. Garg was supported by the Dr. Adam Linton Chair in Kidney Health Analytics. Dr. Khan has received honoraria for speaking engagements from Amgen. Dr. Silver has received an honorarium from Sanofi Canada for speaking engagements.

Acknowledgements: We would like to thank Alexandra Ouedraogo for her assistance with the analysis. Parts of this material are based on data and information compiled and

provided by the Canadian Institutes of Health Information (CIHI), MOH, and MLTC. However, the analyses, conclusions, opinions, and statements expressed herein are those of the author, and not necessarily those of CIHI, MOH, or MLTC. We thank IQVIA Solutions Canada Inc. for use of their Drug Information File.

5.5 References

1. Fried LF, Lee JS, Shlipak M, et al. Chronic Kidney Disease and Functional Limitation in Older People: Health, Aging and Body Composition Study. *J Am Geriatr Soc*. 2006;54(5):750-756. doi:10.1111/j.1532-5415.2006.00727.x

2. Naylor KL, McArthur E, Leslie WD, et al. The three-year incidence of fracture in chronic kidney disease. *Kidney Int*. 2014;86(4):810-818. doi:10.1038/ki.2013.547

3. Coco M, Rush H. Increased incidence of hip fractures in dialysis patients with low serum parathyroid hormone. *American Journal of Kidney Diseases*. 2000;36(6):1115-1121. doi:10.1053/ajkd.2000.19812

4. Alem AM, Sherrard DJ, Gillen DL, et al. Increased risk of hip fracture among patients with end-stage renal disease. *Kidney Int*. 2000;58(1):396-399. doi:10.1046/j.1523-1755.2000.00178.x

5. Mittalhenkle A, Gillen DL, Stehman-Breen CO. Increased risk of mortality associated with hip fracture in the dialysis population. *American Journal of Kidney Diseases*. 2004;44(4):672-679. doi:10.1053/j.ajkd.2004.07.001

6. Downey C, Kelly M, Quinlan JF. Changing trends in the mortality rate at 1-year post hip fracture - a systematic review. *World J Orthop*. 2019;10(3):166-175. doi:10.5312/wjo.v10.i3.166

7. Runesson B, Trevisan M, Iseri K, et al. Fractures and their sequelae in non-dialysis-dependent chronic kidney disease: the Stockholm CREAtinine Measurement project. *Nephrology Dialysis Transplantation*. 2020;35(11):1908-1915. doi:10.1093/ndt/gfz142

8. Nitsch D, Mylne A, Roderick PJ, Smeeth L, Hubbard R, Fletcher A. Chronic kidney disease and hip fracture-related mortality in older people in the UK. *Nephrology Dialysis Transplantation*. 2009;24(5):1539-1544. doi:10.1093/ndt/gfn678

9. Beaubrun AC, Kilpatrick RD, Freburger JK, Bradbury BD, Wang L, Brookhart MA. Temporal trends in fracture rates and postdischarge outcomes among hemodialysis patients. *Journal of the American Society of Nephrology*. 2013;24(9):1461-1469. doi:10.1681/ASN.2012090916

10. Laskowski LK, Goldfarb DS, Howland MA, Kavcsak K, Lugassy DM, Smith SW. A RANKL Wrinkle: Denosumab-Induced Hypocalcemia. *Journal of Medical Toxicology*. 2016;12(3):305-308. doi:10.1007/s13181-016-0543-y

11. Ungprasert P, Cheungpasitporn W, Srivali N, Kittanamongkolchai W, Bischof EF. Life-threatening hypocalcemia associated with denosumab in a patient with moderate renal insufficiency. *Am J Emerg Med*. 2013;31(4):756.e1-756.e2. doi:10.1016/j.ajem.2012.11.011

12. Pittman K, Antill YC, Goldrick A, Goh J, de Boer RH. Denosumab: Prevention and management of hypocalcemia, osteonecrosis of the jaw and atypical fractures. *Asia Pac J Clin Oncol*. 2017;13(4):266-276. doi:10.1111/ajco.12517

13. Block GA, Bone HG, Fang L, Lee E, Padhi D. A single-dose study of denosumab in patients with various degrees of renal impairment. *Journal of Bone and Mineral Research*. 2012;27(7):1471-1479. doi:10.1002/jbmr.1613

14. Jamal SA, Ljunggren Ö, Stehman-Breen C, et al. Effects of denosumab on fracture and bone mineral density by level of kidney function. *Journal of Bone and Mineral Research*. 2011;26(8):1829-1835. doi:10.1002/jbmr.403

15. Langdahl BL, Teglbjærg CS, Ho PR, et al. A 24-Month Study Evaluating the Efficacy and Safety of Denosumab for the Treatment of Men With Low Bone Mineral Density: Results From the ADAMO Trial. *J Clin Endocrinol Metab*. 2015;100(4):1335-1342. doi:10.1210/jc.2014-4079

16. Cummings SR, Martin JS, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *Obstet Gynecol Surv*. 2009;64(12):805-807. doi:10.1097/01.ogx.0000363236.41902.96

17. Agarwal M. Severe Symptomatic Hypocalcemia after Denosumab Administration in an End-Stage Renal Disease Patient on Peritoneal Dialysis with Controlled Secondary Hyperparathyroidism. *Br J Med Med Res*. 2013;3(4):1398-1406. doi:10.9734/bjmmr/2013/2989

18. Kalayanamitra R, Yaghnam I, Patel R, Groff A, Jain R. The Calcium Culprit: A Case of Denosumab-induced Hypocalcemia. *Cureus*. 2019;11(5). doi:10.7759/cureus.4768

19. Ishikawa K, Nagai T, Sakamoto K, et al. High bone turnover elevates the risk of denosumab-induced hypocalcemia in women with postmenopausal osteoporosis. *Ther Clin Risk Manag*. 2016;12:1831-1840. doi:10.2147/TCRM.S123172

20. Dave V, Chiang CY, Booth J, Mount PF. Hypocalcemia post denosumab in patients with chronic kidney disease stage 4-5. *Am J Nephrol*. 2015;41(2):129-137. doi:10.1159/000380960

21. Fizazi K, Carducci M, Smith M, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: A randomised, double-blind study. *The Lancet*. 2011;377(9768):813-822. doi:10.1016/S0140-6736(10)62344-6

22. Watkins KR, Rogers JE, Atkinson B. Tolerability of denosumab in metastatic solid tumor patients with renal insufficiency. *Supportive Care in Cancer*. 2015;23(6):1657-1662. doi:10.1007/s00520-014-2521-8

23. Huynh ALH, Baker ST, Stewardson AJ, Johnson DF. Denosumab-Associated Hypocalcaemia: incidence, severity and patient characteristics in a tertiary hospital setting. *Pharmacoepidemiol Drug Saf*. 2015;25:1274-1278. doi:10.1002/pds

24. Kashyap AS, Kayshap S. Hypoparathyroidism unmasked by alendronate. *Postgrad Med J*. 2000;76(897):417-418. doi:10.1136/pmj.76.897.417

25. Population estimates on July 1st, by age and sex. Accessed March 2, 2020. https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1710000501&pickMembers%5B0%5D=1.7&pickMembers%5B1%5D=2.1

26. Finance OM of. Ontario Population Projections, 2018–2046. Queen's Printer for Ontario. Published 2019. Accessed February 11, 2020. https://www.fin.gov.on.ca/en/economy/demographics/projections/#s3b

27. Langan SM, Schmidt SA, Wing K, et al. The reporting of studies conducted using observational routinely collected health data statement for pharmacoepidemiology (RECORD-PE). *BMJ*. 2018;363:k3532. doi:10.1136/bmj.k3532

28. Cadarette SM, Jaglal SB, Raman-Wilms L, Beaton DE, Paterson JM. Osteoporosis quality indicators using healthcare utilization data. *Osteoporosis International*. 2011;22(5):1335-1342. doi:10.1007/s00198-010-1329-8

29. Diab DL, Watts NB. Bisphosphonate drug holiday: Who, when and how long. *Ther Adv Musculoskelet Dis*. 2013;5(3):107-111. doi:10.1177/1759720X13477714

30. Garg AX, Mamdani M, Juurlink DN, van Walraven C. Identifying individuals with a reduced GFR using ambulatory laboratory database surveillance. *Journal of the American Society of Nephrology*. 2005;16(5):1433-1439. doi:10.1681/ASN.2004080697

31. Levey AS, Stevens LA. Estimating GFR Using the CKD Epidemiology Collaboration (CKD-EPI) Creatinine Equation: More Accurate GFR Estimates, Lower CKD Prevalence Estimates, and Better Risk Predictions. *American Journal of Kidney Diseases*. 2010;55(4):622-627. doi:10.1053/j.ajkd.2010.02.337

32. US Department of Health and Human Services, National Institutes of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE). Published 2017. Accessed November 8, 2022. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50

33. Clemens KK, Jeyakumar N, Alexandra OM, Jenny T, Tayyab K. Bisphosphonate and denosumab initiation in older adults in Ontario , Canada : a population-based cohort study. *Arch Osteoporos*. 2020;133(15).

34. Kim KJ, Hong N, Lee S, Kim M, Rhee Y. A Simple-to-Use Score for Identifying Individuals at High Risk of Denosumab-Associated Hypocalcemia in Postmenopausal Osteoporosis: A Real-World Cohort Study. *Calcif Tissue Int*. 2020;107(6):567-575. doi:10.1007/s00223-020-00754-8

35. Maalouf NM, Heller HJ, Odvina C v., Kim PJ, Sakhaee K. Bisphosphonate-Induced Hypocalcemia: Report of 3 Cases and Review of Literature. *Endocrine Practice*. 2006;12(1):48-53. doi:10.4158/EP.12.1.48

36. Burden AM, Tadrous M, Calzavara A, Cadarette SM. Uptake and characteristics of zoledronic acid and denosumab patients and physicians in Ontario, Canada: impact of drug formulary access. *Osteoporosis International*. 2015;26(5):1525-1533. doi:10.1007/s00198-014-3023-8

37. Vikrant S, Parashar A. Prevalence and severity of disordered mineral metabolism in patients with chronic kidney disease: A study from a tertiary care hospital in India. *Indian J Endocrinol Metab*. 2016;20(4):460-467. doi:10.4103/2230-8210.183457

38. Moe SM, Abdalla S, Chertow GM, et al. Effects of Cinacalcet on Fracture Events in Patients Receiving Hemodialysis: The EVOLVE Trial. *Journal of the American Society of Nephrology*. 2015;26(6):1466-1475. doi:10.1681/ASN.2014040414

39. Rudser KD, de Boer IH, Dooley A, Young B, Kestenbaum B. Fracture Risk after Parathyroidectomy among Chronic Hemodialysis Patients. *Journal of the American Society of Nephrology*. 2007;18(8):2401-2407. doi:10.1681/ASN.2007010022

40. Floege J, Tsirtsonis K, Iles J, Drueke TB, Chertow GM, Parfrey P. Incidence, predictors and therapeutic consequences of hypocalcemia in patients treated with

cinacalcet in the EVOLVE trial. *Kidney Int*. 2018;93(6):1475-1482. doi:10.1016/j.kint.2017.12.014

41. Danese MD, Fox KM, Duryea JL, Desai P, Rubin RJ. The rate, cost and outcomes of parathyroidectomy in the united states dialysis population from 2016–2018. *BMC Nephrol*. 2022;23(1). doi:10.1186/s12882-022-02848-x

42. Ban JK, Hao BB, McCarthy L, Guilcher SJT, Cadarette SM. Denosumab utilization among older adults in Ontario: patient characteristics, persistence with therapy, and return to therapy after an extended gap. *Osteoporosis International*. 2019;30(9):1865-1872. doi:10.1007/s00198-019-05051-1

43. Cromer S, D'Silva KM, Yu EWY, Landon J, Desai R, Kim SC. Temporal Trends in Prescribing of Bone-Directed Therapies in the United States 2009-2020. *J Endocr Soc*. 2021;5:A250-A250.

44. Agirrezabal I, Cabasés JM, di Tanna GL, Sánchez-Iriso E. Inequalities in prescription rates of anti-osteoporosis drugs in primary care in England: A practice-level prescribing data analysis in 2013-2018. *Bone*. 2020;130. doi:10.1016/j.bone.2019.115125

45. Papaioannou A, Morin S, Cheung AM, et al. 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: Summary. *CMAJ*. 2010;182(17):1864-1873. doi:10.1503/cmaj.100771

46. Camacho PM, Petak SM, Binkley N, et al. American association of clinical endocrinologists/American college of endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis-2020 update. *Endocrine Practice*. 2020;26(s1):1-46. doi:10.4158/GL-2020-0524SUPPL

47. Eastell R, Rosen CJ, Black DM, Cheung AM, Murad MH, Shoback D. Pharmacological management of osteoporosis in postmenopausal women: An endocrine society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism*. 2019;104(5):1595-1622. doi:10.1210/jc.2019-00221

48. Compston J, Cooper A, Cooper C, et al. UK clinical guideline for the prevention and treatment of osteoporosis. *Arch Osteoporos*. 2017;12(1). doi:10.1007/s11657-017-0324-5

49. Tsvetov G, Amitai O, Shochat T, Shimon I, Akirov A, Diker-Cohen T. Denosumab-induced hypocalcemia in patients with osteoporosis: can you know who will get low? *Osteoporosis International*. 2020;31(4):655-665. doi:10.1007/s00198-019-05261-7

50. Iskander C, McArthur E, Nash DM, et al. Identifying Ontario geographic regions to assess adults who present to hospital with laboratory-defined conditions: a descriptive study. *CMAJ Open*. 2019;7(4):E624-E629. doi:10.9778/cmajo.20190065

Table 5.1- Selected baseline characteristics of denosumab users, stratified by eGFR and all bisphosphonate users

	Denosumab					Bisphosphonates[b]
	Total N=59,151	**[a]eGFR ≥60 mL/min/1.73 m² N=39,742**	**eGFR 30 - <60 mL/min/1.73 m² N=17,376**	**eGFR 15 - <30 mL/min/1.73 m² N=1,859**	**eGFR <15 mL/min/1.73m² or chronic dialysis N=174**	**Total N=56,847**
Demographics, N (%)						
Mean Age (SD)	79.3 (8.1)	79.3 (8.1)	79.3 (8.1)	79.3 (8.1)	79.2 (7.7)	75.6 (7.3)
Female	53,339 (90.2)	36,058 (90.7)	15,520 (89.3)	1,620 (87.1)	141 (81.0)	42,541 (74.8)
Long Term Care	8,680 (14.7)	4,582 (11.5)	3,612 (20.8)	453 (24.4)	33 (19.0)	1,888 (3.3)
Prescriber Specialty						
Endocrinology	3,727 (6.3)	2,627 (6.6)	966 (5.6)	121 (6.5)	13 (7.5)	1,497 (2.6)
GP/FP	45,942 (77.7)	30,755 (77.4)	13,641 (78.5)	1,421 (76.4)	125 (71.8)	42,481 (74.7)
Geriatric medicine	1,648 (2.8)	1,136 (2.9)	466 (2.7)	46 (2.3)		474 (0.8)
Internal medicine	734 (1.2)	487 (1.2)	218 (1.3)	29 (1.4)		856 (1.5)
Nephrology	46 (0.1)	23 (0.1)	12 (0.1)	11 (0.5)		143 (0.3)
Rheumatology	2,940 (5.0)	2,097 (5.3)	761 (4.4)	68 (3.7)	14 (8.0)	2,970 (5.2)
Other	1,238 (2.1)	816 (2.1)	373 (2.1)	49 (2.4)		1,593 (2.8)
Missing	2,876 (4.9)	1,801 (4.5)	939 (5.4)	124 (6.7)	12 (6.9)	6,833 (12.0)
Comorbidities , N (%)						
CHF	7,076 (12.0)	2,963 (7.5)	3,345 (19.3)	686 (36.9)	82 (47.1)	4,904 (8.6)
Acute Kidney Injury	2,949 (5.0)	668 (1.7)	1,688 (9.7)	518 (27.9)	75 (43.1)	1,789 (3.1)
Diabetes	16,084 (27.2)	9,491 (23.9)	5,539 (31.9)	943 (50.7)	111 (63.8)	15,865 (27.9)
Hypertension	44,482 (75.2)	27,541 (69.3)	15,000 (86.3)	1,776 (95.5)	165 (94.8)	39,124 (68.8)
Syncope	3,473 (5.9)	1,921 (4.8)	1,377 (7.9)	158 (8.5)	17 (9.8)	2,377 (4.2)

Dementia	12,238 (20.7)	6,586 (16.6)	5,023 (28.9)	590 (31.7)	39 (22.4)	5,003 (8.8)
Fall	9,821 (16.6)	5,762 (14.5)	3,532 (20.3)	481 (25.9)	46 (26.4)	6,201 (10.9)
Fragility fractures	13,971 (23.6)	8,705 (21.9)	4,647 (26.7)	565 (30.4)	54 (31.0)	9,434 (16.6)
Mean Charlson Comorbidity Index, mean (SD)	0.78 ± 1.2	0.56 ± 0.99	1.0 ± 1.4	2.1 ± 1.8	3.2± 1.8	0.69 ± 1.2
Medications, N (%)						
Proton pump inhibitors	20,602 (34.8)	12,262 (30.9)	7,315 (42.1)	933 (50.2)	92 (52.9)	15,310 (26.9)
Anticoagulants	6,916 (11.7)	3,373 (8.5)	3,103 (17.9)	413 (22.2)	27 (15.5)	5,070 (8.9)
1,25-OH Vitamin D[c]	572 (1.0)	217 (0.5)	193 (1.1)	108 (5.8)	54 (31.0)	198 (0.3)
Loop diuretics	5,896 (10.0)	2,153 (5.4)	2,960 (17.0)	707 (38.0)	76 (43.7)	3,864 (6.8)
Denosumab	n/a	n/a	n/a	n/a	n/a	337 (0.6)
Oral bisphosphonate	30,883 (52.2)	20,937 (52.7)	9,094 (52.3)	801 (43.1)	51 (29.3)	n/a
Oral steroid	5,821 (9.8)	3,522 (8.9)	2,000 (11.5)	272 (14.6)	27 (15.5)	7,317 (12.9)
Antihypertensive	36,714 (62.1)	22,072 (55.5)	12,897 (74.2)	1,600 (86.1)	145 (83.3)	32,785 (57.7)
Cholinesterase inhibitors	4,001 (6.8)	2,097 (5.3)	1,710 (9.8)	187 (10.1)	7 (4.0)	1,577 (2.8)
Number of Medications, median (IQR)	6 (3-10)	5 (3-9)	8 (5-11)	10 (7-14)	11 (8-15)	5 (2-8)
Health Care Use, mean (SD)						
Family Doctor Visits	12.0 ± 12.5	11.2 ± 11.8	13.36 ± 13.73	16.24 ± 16.54	18.11 ± 19.78	10.08 ± 11.03
Nephrologist visits	0.27 ± 2.5	0.10 ± 1.4	0.30 ± 1.6	1.8 ± 5.6	20 ± 26	0.20 ± 2.0
Endocrinologist visits	0.25 ± 1.0	0.23 ± 0.95	0.25 ± 1.0	0.46 ± 1.3	0.80 ± 2.0	0.18 ± 0.84

Internist visits	2.2 ± 5.7	1.8 ± 5.2	2.6 ± 6.2	4.3 ± 8.7	11.3 ± 15.2	1.8 ± 4.7
Number of hospitalizations	0.50 ± 0.97	0.46 ± 0.91	0.57 ± 1.0	0.82 ± 1.3	1.2 ± 1.6	0.47 ± 0.96
Laboratory Testing						
Number of serum creatinine tests, Mean (SD)	4.4± 6.1	3.74± 5.1	5.4 ± 6.6	9.5 ± 10.6	16.1± 17.2	3.8 ± 5.5
Serum Calcium Measured, N (%)	12,730 (21.5)	7,494 (18.9)	4,350 (25.0)	780 (42.0)	106 (60.9)	9,183 (16.2)
Serum Calcium Value (mmol/L), mean (SD)	2.4 ± 0.12	2.3± 0.12	2.4 ± 0.13	2.4 ± 0.15	2.4± 0.16	2.4 ± 0.13
Ionized Calcium Measured, N (%)	4,323 (7.3)	2,844 (7.2)	1,265 (7.3)	190 (10.2)	24 (13.8)	2,363 (4.2)
Ionized calcium value (mmol/l), mean (SD)	1.2 ± 0.10	1.2 ± 0.08	1.3± 0.11	1.2 ± 0.11	1.2 ± 0.22	1.2 ± 0.11
PTH Measured, N (%)	9,797 (16.6)	6,087 (15.3)	2,894 (16.7)	686 (36.9)	130 (74.7)	5,484 (9.6)
PTH value (pmol/l), Mean (SD)	6.5 ± 7.1	5.1 ± 2.7	7.0 ± 5.6	11.9 ± 10.8	32.4 ± 35.2	7.1 ± 12.3
25-OH,Vitamin D Measured, N (%)	22,370 (37.8)	15,493 (39.0)	6,174 (35.5)	651 (35.0)	52 (29.9)	14,507 (25.5)
25-OH,Vitamin D value (nmol/L), mean (SD)	91.5 ± 33.8	91.5± 34.0	91.7 ± 33.6	90.5 ± 30.2	72.9 ± 30.8	81.2 ± 35.2

Abbreviations eGFR, estimated glomerular filtration rate; SD, standard deviation; PTH, parathyroid hormone; SSRI, selective serotonin reuptake inhibitor; GP/FP, general practitioner/family practitioner

[a]For full baseline characteristics of bisphosphonate users see Supplementary Material F

[b] The most recent eGFR measurement in the 365-day period before the cohort entry date (including the cohort entry date); eGFR was calculated using the Chronic Kidney Disease (CKD)–Epidemiology (EPI) equation: $141 \times \min([\text{serum creatinine concentration in } \mu\text{mol/L}/88.4]/\kappa, 1)^{\alpha} \times \max([\text{serum creatinine concentration in } \mu\text{mol/L}/88.4]/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018$ [if female] × 1.159 [if African-American]; κ=0.7 if female and 0.9 if male; α=-0.329 if female and -0.411 if male; min=the minimum of serum creatinine concentration/κ or 1; max=the maximum of serum creatinine concentration/κ or 1. Information on race was not available in our data sources and all patients were assumed not to be of African-Canadian race; African-Canadians represented less than 5% of the population of Ontario in 2006.

[c] Over the counter vitamin D3 supplement use was not available

Table 5.2- Frequency of calcium testing and cumulative incidence albumin corrected hypocalcemia at 180 days.

		Denosumab % (95%CI)	**Bisphosphonates** % (95%CI)
Calcium Tested**	All Patients	31.8 (31.5, 32.2)	22.5 (22.1, 22.8)
	eGFR ≥60	27.2 (26.8, 27.7)	19.6 (19.2, 20.0)
	eGFR 30 - <60	38.0 (37.3, 38.7)	29.1 (28.3, 29.9)
	eGFR 15-<30	66.5 (64.4-68.6)	64.7 (61.3-67.9)*
	eGFR <15 or maintenance dialysis	92.5 (87.3-96.7)	
Calcium <2.00 mmol/L	All Patients	0.62 (0.56, 0.69)	0.29 (0.25-0.34)
	eGFR ≥60	0.36 (0.31, 0.42)	0.23 (0.19-0.28)
	eGFR 30 - <60	0.69 (0.57, 0.82)	0.37 (0.28-0.48)
	eGFR 15-<30	3.5 (2.7, 4.4)	2.40 (1.5-3.7)*
	eGFR <15 or maintenance dialysis	24 (18, 31)	
Calcium <1.80 mmol/L	All Patients	0.22 (0.18, 0.26)	0.09 (0.07-0.12)
	eGFR ≥60	0.08 (0.06, 0.12)	0.07 (0.05-0.10)
	eGFR 30 - <60	0.24 (0.17, 0.32)	0.12 (0.07-0.19)*
	eGFR 15-<30	1.56 (2.07-2.20)	
	eGFR <15 or maintenance dialysis	14.9 (10.1-20.7)	

*groups combined due to small event rates

**Median time to first calcium test was 54 days (25^{th}, 75^{th} percentile 15, 113)

Table 5.3- Predictive modelling for the probability of mild hypocalcemia within 180 days.

Variable	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Age, per year	0.98 (0.97, 1.00)	0.95 (0.93, 0.98)
Sex, male	1.06 (0.77, 1.45)	0.72 (0.38, 1.37)
eGFR, continuous	0.97 (0.96, 0.97)**	0.90 (0.87, 0.93)
Calcitriol use	1.63 (1.02, 2.61)	1.12 (0.64, 1.96)**
Bisphosphonate use*	0.70 (0.57, 0.86)	0.54 (0.31, 0.95)
Baseline calcium 2.2-2.4 mmol/L	0.45 (0.31, 0.65)	-
Baseline calcium >2.4 mmol/L	0.32 (0.21, 0.47)	-
Baseline calcium missing	0.13 (0.09, 0.19)	-
PTH <7 pmol/L	0.29 (0.16, 0.53)	0.31 (0.11, 0.82)
PTH 7-<14 pmol/L	0.47 (0.26, 0.84)	0.51 (0.24, 1.08)
PTH >21 pmol/L	1.04 (0.55, 1.97)	0.58 (0.27, 1.27)
PTH missing	0.43 (0.26, 0.73)	0.74 (0.37, 1.47)
25 hydroxyvitamin D >75 nmol/L	0.64 (0.45, 0.90)	-
25 hydroxyvitamin D missing	0.92 (0.68, 1.25)	-
Baseline calcium, continuous (per 0.1mmol/L increase)	-	0.73 (0.63, 0.86)

Model 1: Entire Denosumab cohort; Model 2: Individuals with eGFR <30ml/min/1.73m^2 who had a baseline calcium measured

*bisphosphonate use was defined as a prescription filled in the year prior to, and not overlapping with, a denosumab prescription

** There was some evidence of non-proportionality of hazards with eGFR in the model 1 and calcitriol in model

Chapter 6

6 Conclusion

6.1 Main findings

In this current work we investigated risk factors for and prediction and treatment of fractures in individuals with chronic kidney disease (CKD).

We created a simple-to-use fracture risk prediction calculator, targeted specifically to individuals receiving maintenance dialysis. We found that age, sex, and previous fracture were strong risk factors for fracture, similar to studies in the general population. The addition of other, dialysis-specific risk factors including parathyroid hormone (PTH), history of renal transplant, serum albumin, and proton pump inhibitor use also improved the model performance. The model showed good calibration and discrimination at 1 year and moderate discrimination at 3 years.

We then examined sodium glucose cotransporter 2 inhibitors (SGLT-2i) as another potential risk factor for fracture in people with CKD. In a cohort of over 35,000 patients who were newly prescribed SGLT-2i, we did not find an increased risk of fracture compared to those prescribed dipeptidyl peptidase IV inhibitors. When analyzed by estimated glomerular filtration rate (eGFR) category, we observed no interaction between kidney function and SGLT-2i. Assessing its risk profile is particularly important in those with CKD as this class of medications is being used more and more for its renoprotective benefits.[2]

Finally, we assessed the risk of hypocalcemia with denosumab, a medication being increasingly used to reduce fracture risk in individuals with CKD.[3] We found that only one third of individuals had their serum calcium value measured before or after denosumab administration, much lower than that suggested in the product monograph and clinical guidelines. We also observed that the incidence of hypocalcemia increased significantly as the eGFR dropped below 30 ml/min/1.73m^2, and one quarter of those with an eGFR <15 ml/min/1.73m^2 had a calcium value below 2.0 mmol/L.

6.2 General Strengths and limitations

The three projects above have several common strengths. First, by leveraging routinely collected data, we were able to include a large number of patients-i.e. over 11,000 patients receiving dialysis in a fracture risk prediction model and over 59,000 patients who filled a prescription for denosumab. This translated to large numbers of events (for example 839 fractures were observed in the fracture risk prediction study) increasing the power of the studies. Second, our studies included patients who were more reflective of the real-world population compared to those included in clinical trials. That is, we were able to include patients more comorbidities, and live in more rural or remote communities.[4] For example, the patients included in the study of hypocalcemia after denosumab were older, had a higher prevalence of long-term care usage, and a higher prevalence of severe CKD than patients who were included in the original efficacy trials.[5] Third, all three studies had low loss to follow up, which only occurred when a person emigrated from the province, which happens at a rate of less than 1% per year.[6]

There are also several shared limitations among the studies. While codes used to define fragility fractures overall were both sensitive and specific, the codes used specifically to define vertebral fractures had lower sensitivity.[7] As a result, vertebral fractures were likely underreported in these studies.

There are some other constraints resulting from the use of administrative databases. We lacked information on certain well described risk factors for fragility fracture from the general population such as body mass index and family history of fracture.[8] Also, bone mineral density was also not available in the databases used, preventing its inclusion in both the fracture prediction tool as well as the propensity score used to balance groups in the study of SGLT-2i. However, the exclusion of bone mineral density from the fracture risk prediction score did increase the practical nature of the score and eliminates the need for extra medical visits for patients receiving dialysis.

Finally, risk prediction models were limited by missing data. In the study of hypocalcemia after denosumab, 83% and 62% of PTH and vitamin D levels were missing, which precluded their inclusion. In the fracture risk prediction model

approximately 23% of participants were missing at least one of calcium, albumin or phosphate value(s). Based on the missingness patterns and typical dialysis practice patterns and guidelines we suspect that this was likely due to differences in lab availability rather than differences in the frequency of lab measurement.[9,10] While this may have affected the prediction, a sensitivity analysis done using complete case analysis yielded similar results.

6.3 Implications and Future Directions

Fragility fractures in individuals with CKD are common and often associated with poor outcomes; despite this, our understanding how to predict and mitigate this risk is limited. In this thesis, we explored risk factors for fracture, including commonly prescribed medications as well as creating an easy-to-use risk prediction score for patients receiving maintenance dialysis. We also explored a previously described but poorly quantified side effect of denosumab, a medication that is commonly used to decrease the risk of fracture.

Further research is needed in several areas. Firstly, refining the ability to identify individuals with CKD who are at highest risk of fracture and might benefit most from interventions (e.g. pharmacotherapy). This includes conducting an external validation of the above fracture risk prediction score as well as an extension of the score to those with severe non-dialysis dependent CKD and to recipients of kidney transplants. Secondly, a rigorous prospective assessment of the utility of bone mineral density in those with severe kidney disease (i.e. eGFR <30 ml/min/1.73m^2) is needed. Finally, further high-quality trials of the efficacy of denosumab in preventing fractures in individuals with an eGFR <30 ml/min/1.73m^2 is also needed, particularly for individuals receiving dialysis, for whom other treatment options are limited.

6.4 References

1. Ting QC, Haonan L, Huawei Z, Yan PC. Risk of Fractures Associated with Dipeptidyl Peptidase-4 Inhibitor Treatment: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Diabetes Therapy*. 2019;10:1879-1892. doi:10.6084/m9.figshare.8846225

2. KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. *Kidney Int*. 2020;98(4):S1-S115. doi:10.1016/j.kint.2020.06.019

3. Cromer S, D'Silva KM, Yu EWY, Landon J, Desai R, Kim SC. Temporal Trends in Prescribing of Bone-Directed Therapies in the United States 2009-2020. *J Endocr Soc*. 2021;5:A250-A250.

4. Smyth B, Haber A, Trongtrakul K, et al. Representativeness of Randomized Clinical Trial Cohorts in End-stage Kidney Disease: A Meta-analysis. *JAMA Intern Med*. 2019;179(10):1316-1324. doi:10.1001/jamainternmed.2019.1501

5. Cummings SR, Martin JS, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *Obstet Gynecol Surv*. 2009;64(12):805-807. doi:10.1097/01.ogx.0000363236.41902.96

6. Finance OM of. Ontario Population Projections, 2018–2046. Queen's Printer for Ontario. Published 2019. Accessed February 11, 2020. https://www.fin.gov.on.ca/en/economy/demographics/projections/#s3b

7. Lisa M Lix, Mahmoud Azimaee, Beliz Acan Osman, et al. Osteoporosis-related fracture case definitions forpopulation-based administrative data. *BMC Public Health*. 2010;10. doi:10.1186/1471-2458-10-792

8. Leslie WD, Lix LM, Langsetmo L, et al. Construction of a FRAX® model for the assessment of fracture probability in Canada and implications for treatment. *Osteoporosis International*. 2011;22(3):817-827. doi:10.1007/s00198-010-1464-2

9. Iskander C, McArthur E, Nash DM, et al. Identifying Ontario geographic regions to assess adults who present to hospital with laboratory-defined conditions: a descriptive study. *CMAJ Open*. 2019;7(4):E624-E629. doi:10.9778/cmajo.20190065

10. Kettler M, Leonard MB, on behalf of the Work Group. KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD). Published 2017. Accessed October 7, 2022. https://kdigo.org/guidelines/ckd-mbd/

Appendix A

Supplementary Material for “Fracture Risk Prediction in Patients”

Appendix A.A TRIOPD STATEMENT

Section/Topic			Checklist Item	Page
Title and abstract				
Title	1	);V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	title
Abstract	2	);V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	abstract
Introduction				
Background and objectives	3a	);V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	Introduction
	3b	);V	Specify the objectives, including whether the study describes the development or validation of the model or both.	Introduction
Methods				
Source of data	4a	);V	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
	4b	);V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	Methods
Participants	5a	);V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	Methods
	5b	);V	Describe eligibility criteria for participants.	Methods
	5c	);V	Give details of treatments received, if relevant.	n/a
Outcome	6a	);V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	Methods
	6b	);V	Report any actions to blind assessment of the outcome to be predicted.	Methods
Predictors	7a	);V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	Methods
	7b	);V	Report any actions to blind assessment of predictors for the outcome and other predictors.	Methods
Sample size	8	);V	Explain how the study size was arrived at.	Methods
Missing data	9	);V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	Methods
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	Methods
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	Methods
	10c	V	For validation, describe how the predictions were calculated.	Methods
	10d	);V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	Methods
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	Methods
Risk groups	11	);V	Provide details on how risk groups were created, if done.	n/a
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	Methods
Results				
Participants	13a	);V	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.	Appendix
	13b	);V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including	Results

			the number of participants with missing data for predictors and outcome.	
	3c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	n/a
Model development	4a	D	Specify the number of participants and outcome events in each analysis.	Table 2
	4b	D	If done, report the unadjusted association between each candidate predictor and outcome.	n/a
Model specification	5a	D	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).	Appendix
	5b	D	Explain how to the use the prediction model.	Results
Model performance	16	);V	Report performance measures (with CIs) for the prediction model.	Results
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	n/a
Discussion				
Limitations	18	);V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	Discussion
Interpretation	9a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	Discussion
	9b	);V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	Discussion
Implications	20	);V	Discuss the potential clinical use of the model and implications for future research.	Discussion
Other information				
Supplementary information	21	);V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	Appendix
Funding	22	);V	Give the source of funding and the role of the funders for the present study.	Funding

Appendix A.B- Databases used to obtain baseline information

Database	Description
Ontario Health Insurance Plan (OHIP)	Diagnostic information and health claims for inpatient and outpatient physician services.
Ontario Drug Benefit (ODB)	Highly accurate records of all dispensed outpatient prescriptions covered through the Ontario Drug Benefit program, including corticosteroids and proton pump inhibitors
Canadian Institute for Health Information Discharge Abstract Database/ Same Day Surgery (CIHI-DAD/SDS)	Diagnostic and procedural information for all hospitalizations and same day surgeries.
Canadian Institute for Health Information National Ambulatory Care Reporting System (NACRS)	Information on emergency department visits.
ICES-derived Physician Database (IPDB)	Physician related information such as birth date, sex, education, and specializations.
Registered Persons Database (RPDB)	Information on vital patient statistics including sex, birth and death dates for all residents who have been issued a health card
Local Health Integration Network (LHIN)	Information on the geographical location of participants
Canadian Organ Replacement Registry (CORR)	Provides information on recipients of dialysis and renal transplant
Ontario Marginalization Index (ONMARG)	Information on residential instability, material deprivation and dependency based on geographic area
Ontario Renal Reporting System (ORRS)	Information on individuals with chronic kidney disease and end stage kidney disease
Ontario Lab Information System (OLIS)	Laboratory test orders and results from hospitals, community labs, and public health labs.

Appendix A.C- Codes used to obtain baseline and covariate information

Condition	OHIP Feecode	OHIP Diagnostic Code	ICD10
Kidney Transplant	S435, S434		
Hip Fracture			S722, S721, S720
Spinal Fracture		805	S220, S221, S320, S327, S328
Shoulder or upper arm fracture		812	S422
Wrist or Forearm Fracture		813	813
Pelvis or hip fracture		808	S321, S322, S324, S325, S327, S328
Chronic liver disease	Z551, Z554	571, 573, 070	4561, 4562, 070, 5722, 5723, 5724, 5728, 573, 7824, V026, 571, 2750, 2751, 7891, 7895
Diabetes	K045, K046, K029, K030, Q040	250,	E10, E11, E13, E14
Rheumatoid Arthritis		714	M05, M06
OHIP- Ontario Health Insurance Plan; ICD- International Classification of Diseases; CCI- Canadian Classification of health Interventions;			

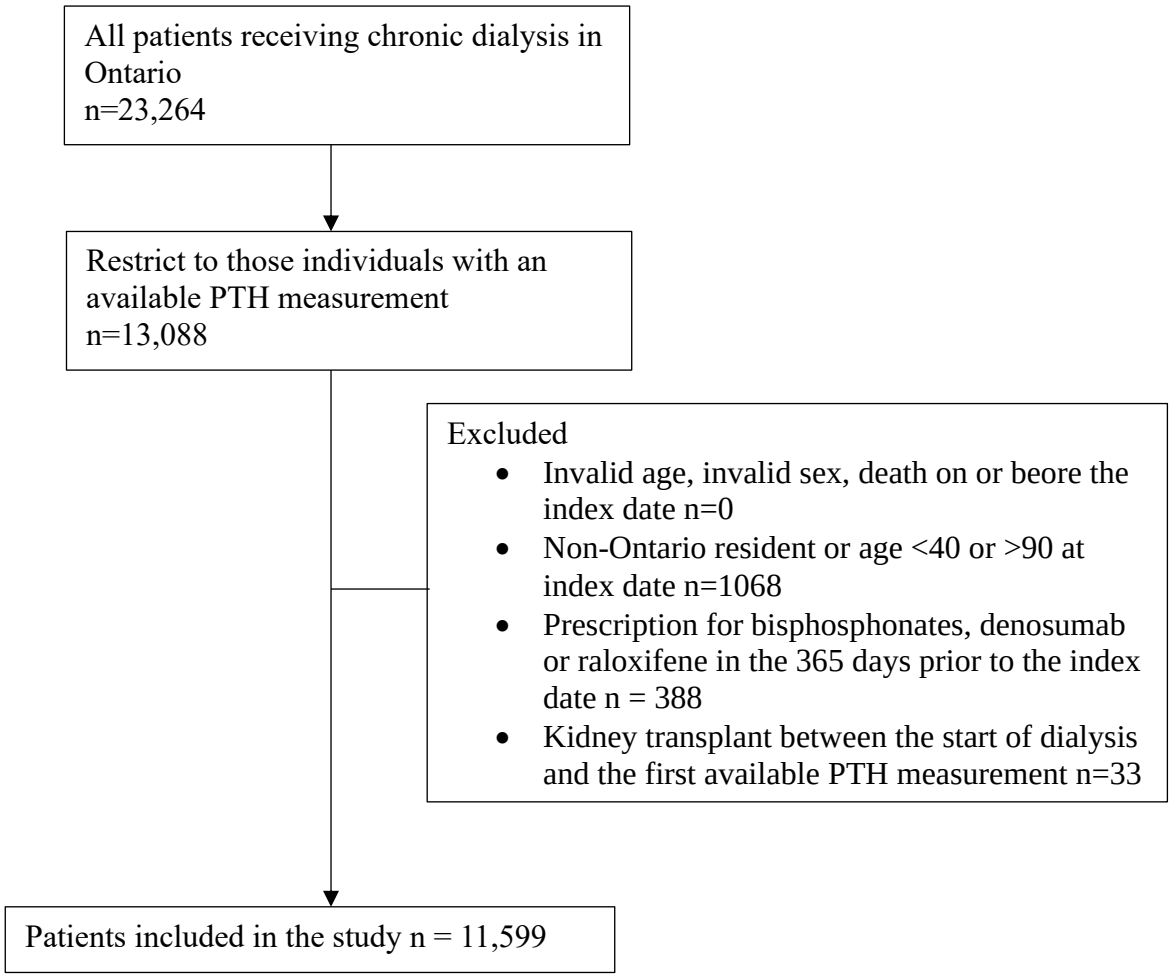
Appendix A.D- Drug Identification Numbers

Medication Class	DINs Used
Bisphosphonates	00582522, 01927051, 01927078, 01974491, 01997629, 02059762, 02059770, 02059789, 02176017, 02201011, 02201038, 02233055, 02239146, 02242518, 02242725, 02244550, 02244551, 02244552, 02245329, 02245330, 02245828, 02246599, 02246896, 02247323, 02247373, 02248296, 02248625, 02248686, 02248728, 02248730, 02249669, 02249677, 02249685, 02258102, 02258110, 02261715, 02263866, 02264951, 02264978, 02264986, 02269198, 02270129, 02273179, 02275279, 02276429, 02284006, 02286335, 02288087, 02288109, 02298376, 02298384, 02298392, 02299712, 02302209, 02314940, 02316838, 02319861, 02324199, 02327295, 02352966, 02353687, 02357984, 02368552, 02370255, 02370417, 02377721, 02381486, 02381494, 02384701, 02384728, 02385031, 02388545, 02388553, 02394863, 02394871, 02397773, 02401606, 02403633, 02403641, 02406306, 02407639, 02408082, 02411407, 02413701, 02413809, 02415100, 02415186, 02421550, 02422425, 02422433,

	02424177, 02428725, 02428733, 02429160, 02434458, 02442760, 02444739, 02454467, 02454475, 02485184, 09854534, 09854639, 09857301, 09857304, 09857305, 09857399, 09857402, 09857403
Denosumab	02343541, 02368153
Corticosteroids	09857797, 09857798, 09857799, 00015016, 00015024, 00016438, 00016446, 00016462, 00021695, 00028185, 00030910, 00030929, 00030988, 00036129, 00036366, 00093629, 00210188, 00232378, 00249963, 00252417, 00271373, 00280437, 00285471, 00295094, 00312770, 00349100, 00354309, 00489158, 00501050, 00504416, 00550957, 00598194, 00610623, 01964070, 01964968, 01964976, 02194082, 02194090, 02229293, 02240684, 02240687, 02250055, 02261081, 02279363, 02470632, 09854537
Estrogens	00002569, 00002577, 00002585, 00003352, 00003360, 00003379, 00013587, 00013781, 01904426, 01904434, 02091461, 02100304, 00108278, 02061031, 00017965, 00017973, 02108186, 02241835, 02241837, 02242531, 02242878, 02242879, 02243529, 02243530, 00022632, 00024007, 00028630, 00028681, 00030333, 00340758, 00340766, 00340847, 00343536, 00373265, 00373273, 00538582, 00538590, 00620947, 00695734, 00782424, 02188724, 02188732, 02410788, 02410796, 02486296, 02486318, 00002569, 00002577, 00002585, 00002593, 00028215, 00028223, 00028231, 00029238, 00265470, 00265489, 00282677, 00282685, 00403466, 00464791, 00464805, 00716758, 00756792, 00756849, 00756857, 02016958, 02043394, 02043408, 02043424, 02089769, 02089777, 02089793, 02148587, 02148595, 02204401, 02204428, 02204436, 02204444, 02225190, 02231509, 02231510, 02237807, 02237808, 02238704, 02243722, 02243724, 02243999, 02244000, 02244001, 02244002, 02245676, 02246967, 02246968, 02246969, 02247499, 02414678, 02414686, 02414694, 02449048, 02449056, 02449064
Testosterone	00005622, 00005630, 00029246, 00030783, 00030902, 00782327, 00985007, 01977571, 02239653, 02245345, 02245346, 02245972, 02280248, 02322498, 02463792, 02463806, 09850325, 09850511, 09852271, 09852514, 09853006
Aromatase inhibitors	00587729, 02128209, 02224135, 02231384, 02242705, 02309114, 02313049, 02320738, 02322315, 02328690, 02338459, 02338467, 02339080, 02343657, 02344815, 02347997, 02348969, 02351218, 02358514, 02361418, 02365650, 02372169, 02372282, 02373009, 02373424,

	02374420, 02379104, 02379562, 02390183, 02393573, 02394898, 02404400, 02404990, 02407841, 02408473, 02417855, 02419726, 02421585, 02427818, 02428156, 02442736, 02458799, 02459884
Proton pump inhibitors	00000100, 00846503, 02119579, 02165503, 02165511, 02190915, 02229453, 02230737, 02243796, 02243797, 02244522, 02245058, 02249472, 02260867, 02267233, 02280515, 02280523, 02285487, 02292920, 02293811, 02293838, 02295415, 02296446, 02296632, 02296640, 02298074, 02298082, 02299585, 02300486, 02300524, 02301083, 02305046, 02307871, 02308703, 02309866, 02310260, 02310805, 02310813, 02314177, 02314185, 02320614, 02320622, 02320851, 02329433, 02345579, 02345587, 02348691, 02353830, 02353849, 02356511, 02356538, 02357054, 02357682, 02357690, 02370808, 02374870, 02381737, 02381745, 02385449, 02385457, 02385643, 02385651, 02385767, 02395258, 02395266, 02402610, 02402629, 02403617, 02408392, 02408406, 02408570, 02410389, 02411857, 02412969, 02415208, 02416549, 02416565, 02417448, 02420198, 02422638, 02422646, 02428164, 02428180, 02432404, 02433001, 02433028, 02437945, 02439549, 02440628, 02441853, 02466147, 02467372, 02471825, 09857195, 09857267, 09857285, 09857314, 09857341, 09857342, 09857343, 09857464, 09857500, 09857530, 09857536, 09857640
Activated Vitamin D	00002690, 00003093, 00009830, 00033057, 00033545, 00434493, 00474517, 00474525, 00481815, 00481823, 00630934, 00759546, 00824291, 00891738, 00891746, 01928406, 01928422, 02017598, 02017601, 02229879, 02240329, 02242502, 02243790, 02245686, 02399334, 02399342, 02431637, 02431645, 02485710, 02485729, 02495899, 02495902, 09857482, 09857483, 09857836, 09857837, 09857882, 80003615

Appendix A.E- Cohort Build

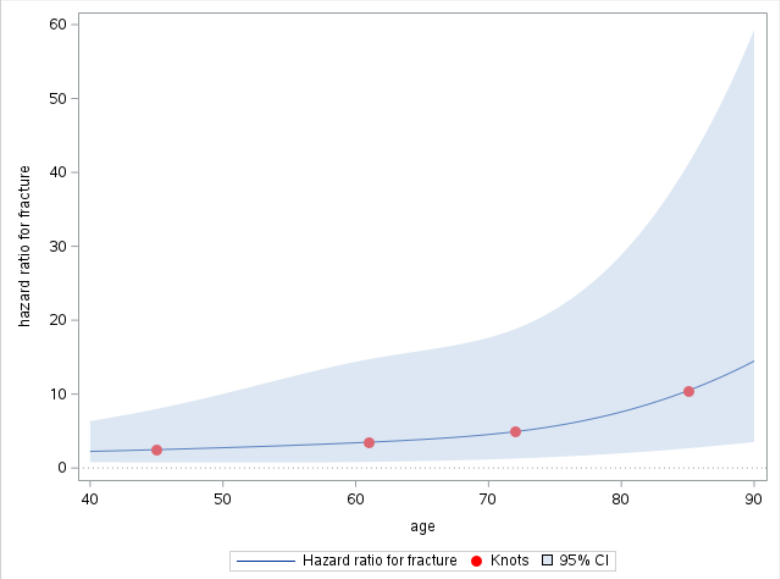


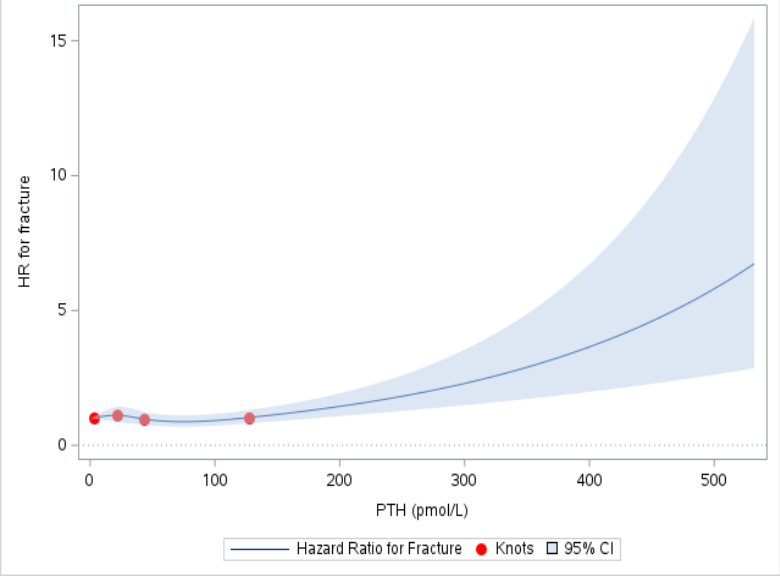
Appendix A.F- Patterns of Missing Data

Serum Calcium	Serum Phosphate	Serum Albumin	Frequency (%)	Group Means		
				Calcium) (mmol/L	Phosphate (mmol/L)	Albumin (g/L)
X	X	X	8856 (76.35)	2.35	1.60	35.3
X	X	.	72* (0.62)	2.18	1.19	.
X	.	X		2.32	.	36.0
.	X	X	193 (1.66)	.	1.66	36.0
.	X	.	136 (1.17)	.	1.51	.
.	.	X	155 (1.34)	.	.	37.5
.	.	.	2187 (18.86)	.	.	.

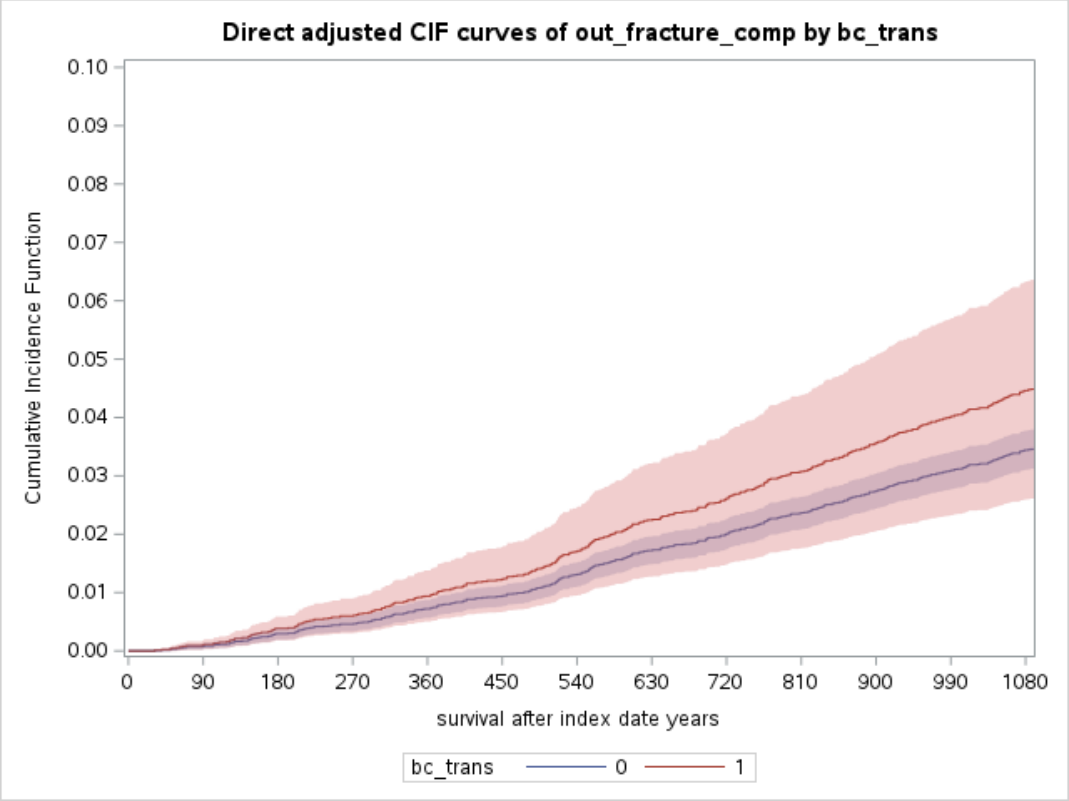
* cells combined due to low numbers, in accordance with ICES policies
X- available values
.- missing values

Appendix A.G- Hazard Ratio for fracture by age and parathyroid hormone level





Appendix A.H- Cumulative incidence of fracture by transplant status after adjustment for other model covariates



Appendix A.I- Sensitivity and specificity of the model

Cut-off	Sensitivity	Specificity
3-year prediction		
5%	32%	87%
4%	44%	78%
3%	65%	58%
1-year prediction		
2%	15%	97%
1%	43%	84%
0.50%	87%	35%

Appendix B

Supplementary Material for "Fracture Risk of Sodium Glucose Cotransporter-2 Inhibitors in Chronic Kidney Disease"

Appendix B.A- RECORD PE Statement

Item No	STROBE items	RECORD items	RECORD-PE 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 geographical region and timeframe 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.	—	Abstract
Introduction				
Background rationale				
2	Explain the scientific background and rationale for the investigation being reported.	—	—	Introduction
Objectives				
3	State specific objectives, including any prespecified hypotheses.	—	—	Introduction
Methods				

Study design				
4	Present key elements of study design early in the paper.	—	4.a: Include details of the specific study design (and its features) and report the use of multiple designs if used. 4.b: The use of a diagram(s) is recommended to illustrate key aspects of the study design(s), including exposure, washout, lag and observation periods, and covariate definitions as relevant.	Methods: Study Design and Setting
Setting				
5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection.	—	—	Methods: Study Design and Setting
Participants				
6	(a) Cohort study—give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. Case-control study—give the eligibility criteria, and the sources and methods of	6.1: The methods of study population selection (such as codes or algorithms used to identify participants) 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	6.1.a: Describe the study entry criteria and the order in which these criteria were applied to identify the study population. Specify whether only users with a specific indication were included and	Methods: Population Appendix D and G

	case ascertainment and control selection. Give the rationale for the choice of cases and controls. Cross sectional study—give the eligibility criteria, and the sources and methods of selection of participants. (b) Cohort study—for matched studies, give matching criteria and number of exposed and unexposed. Case-control study—for matched studies, give matching criteria and the number of controls per case.	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.	whether patients were allowed to enter the study population once or if multiple entries were permitted. See explanatory document for guidance related to matched designs.	
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.	7.1.a: Describe how the drug exposure definition was developed. 7.1.b: Specify the data sources from which drug exposure information for individuals was obtained. 7.1.c: Describe the time window(s) during which an individual is considered exposed to the drug(s). The	Methods: Population, Patient Characteristics, and Outcomes Appendices: C, D, and E

			rationale for\ selecting a particular time window should be provided. The extent of potential left truncation or left censoring should be specified. 7.1.d: Justify how events are attributed to current, prior, ever, or cumulative drug exposure. 7.1.e: When examining drug dose and risk attribution, describe how current, historical or time on therapy are considered. 7.1.f: Use of any comparator groups should be outlined and justified. 7.1.g: Outline the approach used to handle individuals with more than one relevant drug exposure during the study period.	
Data sources/measurement				
8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of		8.a: Describe the healthcare system and mechanisms for generating the drug exposure records. Specify the care setting in which the	Methods: Data Sources, Population, Patient Characteristics, and Outcomes

	assessment methods if there is more than one group.		drug(s) of interest was prescribed.	Appendices: B, C, D, and E
Bias				
9	Describe any efforts to address potential sources of bias.	—	—	Methods: Statistical Analysis
Study size				
10	Explain how the study size was arrived at.	—	—	Results Appendix G
Quantitative variables				
11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why.	—	—	Methods: Statistical Analysis
Statistical methods				
	(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) Cohort study—if applicable, explain how loss to follow-up was addressed. Case-control study—if applicable, explain how matching of cases and controls was	—	12.1.a: Describe the methods used to evaluate whether the assumptions have been met. 12.1.b: Describe and justify the use of multiple designs, design features, or analytical approaches.	Methods: Statistical Analysis

	addressed. Cross sectional study—if applicable, describe analytical methods taking account of sampling strategy. (e) Describe any sensitivity analyses.			
Data access and cleaning methods				
12	—	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: Population, and Data Sources Data access/access to data analysis protocol
Linkage				
12	—	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 the numbers of individuals at eachstage of the study (eg, numbers potentially eligible, examined for eligibility, confirmed eligible, included	13.1: Describe in detail the selection of the individuals included in the study (that is, study population selection) including filtering based on data quality, data availability, and linkage. The selection of included individuals can be described in the	—	Results Appendix G

	in the study, completing follow-up, and analysed). (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram.	text or by means of the study flow diagram.		
Descriptive data				
14	(a) Give characteristics of study participants (eg, demographic, clinical, social) and information on exposures and potential confounders. (b) Indicate the number of participants with missing data for each variable of interest. (c) Cohort study—summarise follow-up time (eg, average and total amount).	—	—	Results Table 1 Appendices: H and I
Outcome data				
15	Cohort study—report numbers of outcome events or summary measures over time. Case-control study—report numbers in each exposure category, or summary measures of exposure. Cross sectional study—	—	—	Results Table 3

	report numbers of outcome events or summary measures.			
Main results				
16	(a) Give unadjusted estimates and, if applicable, confounder adjusted estimates and their precision (eg, 95% confidence intervals). Make clear which confounders were adjusted for and why they were included. (b) Report category boundaries when continuous variables are categorised. (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period.	—	—	Results Table 3 Appendix F
Other analyses				
17	Report other analyses done—eg, analyses of subgroups and interactions, and sensitivity analyses.	—	—	Results Table 4
Discussion				
Key results				
18	Summarise 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.	19.1.a: Describe the degree to which the chosen database(s) adequately captures the drug exposure(s) of interest.	Discussion
Interpretation				
20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	—	20.a: Discuss the potential for confounding by indication, contraindication or disease severity or selection bias (healthy adherer/sick stopper) as alternative explanations for the study findings when relevant.	Conclusion
Generalisability				
21	Discuss the generalisability (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
Accessibility of protocol, raw data, and programming code				

22	—	22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	—	Data access/access to data analysis protocol

*REFERENCE: Langan SM, Schmidt S, Wing K, Ehrenstein V, Nicholls S, Filion K, Klungel O, Petersen
I, Sorensen H, Guttmann A, Harron K, Hemkens L, Moher D, Schneeweiss S, Smeeth L, Sturkenboom
M, von Elm E, Wang S, Benchimol EI. The REporting of studies Conducted using Observational

Appendix B.B- Descriptions of databases used to obtain demographic, comorbid condition and outcome data

Database	Description
Canadian Institute for Health Information Discharge Abstract Database/ Same Day Surgery (CIHI-DAD/SDS)	Diagnostic and procedural information for all hospitalizations and same day surgeries.
Ontario Lab Information System (OLIS)	Laboratory test orders and results from hospitals, community labs, and public health labs.
ICES-derived Physician Database (IPDB)	Physician related information such as birth date, sex, education, and specializations.
Canadian Institute for Health Information National Ambulatory Care Reporting System (NACRS)	Information on emergency department visits.
Ontario Drug Benefit (ODB)	Highly accurate records of all dispensed outpatient prescriptions covered through the Ontario Drug Benefit program, including domperidone and metoclopramide.
Ontario Health Insurance Plan (OHIP)	Diagnostic information and health claims for inpatient and outpatient physician services.
Office of the Registrar General- Deaths (ORDG)	Cause of death information extracted from death certificates
Registered Persons Database (RPDB)	Information on vital patient statistics including sex, birth and death dates for all residents who have been issued a health card

Appendix B.C- Codes used to obtain information about baseline measures and the databases used to obtain the information

Variable	Database	Codes Used
Age	RPDB	
Sex	RPDB	
Location of residence- rural status	RPDB	RURAL
Socioeconomic status (neighbourhood income quintiles)	RPDB	INCQUINT
Index Year	ODB	
Residential Status- Long term care	ODB	LTC=1
Prescribing physician	IPDB	MAINSPECIALTY
Duration of Diabetes	CIHI-DAD OHIP	OHIP Feecode: K045, K046, K029 K030, Q040 OHIP Diagnostic Code: 250 ICD10: E10, E11, E13, E14 ODD: Diagdate-index date
Fragility Fracture	CIHI DAD NACRS OHIP	ICD10: S720, S721, S722, S220, S221, S320, S327, S328, S422, S520-S529, S321, S323-S328 OHIP Diagnostic code: 805, 808, 812, 813
Previous fall	CIHI-DAD NACRS	S220, S221, S320, S327, S328 OHIP Diagnostic code: 805
Major cancer	CIHI-DAD OHIP	ICD10: S422 OHIP Diagnostic Code: 812
Dementia	CIHI-DAD OHIP	ICD10: S520-S529 OHIP Diagnostic Code: 813
Rheumatoid arthritis	CIHI-DAD OHIP	S321, S323-S328 OHIP Diagnostic Code: 808
Osteoporosis	CIHI-DAD OHIP	OHIP Diagnostic Code: 733 ICD10 M80-M82
Hypertension	CIHI-DAD OHIP	OHIP Diagnostic Code: 401-405 ICD10: I10-13, I15 HYPERTENSION: DIAGATE
Hypotension	CIHI-DAD	ICD10: I95
Coronary artery disease (excluding angina)	CIHI-DAD OHIP	OHIP Feecode: R741-743, G298, E646, E651, E652, E654, E655, Z434, Z448 OHIP Diagnostic Coe: 410, 412 ICD10: I21, I22, Z955, T822 CCI: 1IJ50, 1IJ76
Arrhythmia	CIHI-DAD OHIP	OHIP Feecode: G178, G179, G249, G259, G261, Z431, Z437, Z443

		ICD10: I44, I45, I47, I48, I4900, I4901, I491-I494, !498, !499, R000, R001
Diabetic retinopathy	CIHI-DAD	ICD10: E1030-E1033, E1130-E1133, E1330-E1333, E1430-E1433, H360
Diabetic neuropathy	CIHI-DAD	ICD10: E1040-1042, E1048, E1049, E1440-E1442, E1448, E1140-E1242, E1148, E1340-E1342, E1348, G590, G632, G990
Hypoglycemia	CIHI-DAD NACRS	ICD10: E15, E160-E162, E1063, E1163, E1363, E1463
Peripheral vascular disease	CIHI-DAD OHIP	OHIP Feecode: R787, R780, R797, R804, R809, R875, R815, R936, R783-R785, E626, R814, R786, R937, R860, R861, R855, R856, R933, R934, R791, E672, R794, R813, R867, E649 ICD10: I700, I702, I708, !709, !731, 1738, I739, K551 CCI: 1KA76, 1KA50, 1KE76, 1KG50, 1KG57, 1KG76MI, 1KG87, 1IA87LA, 1IB87LA, 1IC87LA, 1ID87LA, 1KA87LA, 1KE57
Liver disease	CIHI-DAD OHIP	OHIP Feecode: Z551, Z554 OHIP Dx Code: 571, 573, 070 ICD10: B16-19, I85, R17, R18, R160, R162, B942, Z225, E831, E830, K70, K713-K715, K717, K721, K729, K73, K74, K753, K754, K758, K759, K76, K77
COPD	CIHI-DAD COPD	ICD10: J41, J43, J44 COPD DIAGDATE
CHF	CIHI-DAD OHIP CHF	OHIP Diagnostic Code: 428 ICD10: I500, I501, I509 DIAGDATE
Hypothyroidism	CIHI-DAD	ICD10: E00, E01, E02, E03, E890
Disorder of calcium metabolism/dietary calcium deficiency	CIHI-DAD	ICD10: E58, E835
Stroke/TIA	CIHI-DAD OHIP NACRS	OHIP diagnostic Code: 436, 432, 435 ICD10: I60, I61, I600-I619, I630-I635, I638, I639, I64, H342, G450-G453, G459, H340
Syncope	CIHI-DAD	ICD10: R55
Alcohol misuse	CIHI-DAD	ICD10: E244, E512, E52, F10, G312, G621, G721, I426, K292, K70, K860, T51, X45, X65, Y15, Y573, Z502, Z714, Z721
Medication Use	ODB	
Hemoglobin A1C	OLIS	OBSERVATIONCODE: 4548-4, 71875-9, 59261-8, 17855-8, 17856-6, 41995-2
ACR (mg/mmol)	OLIS	OBSERVATIONCODE: 14959-1, 30000-1, 32294-1, XON10383-8, XON12394-3
Diabetes management	OLIS OHIP	OHIP Feecode: K030, Q040, K045, K046 OHIP Diagnostic code: K046

GP/FP visits	IPDB	Mainspeciality = "GP/FP" or "F.P./EMERGENCY MEDICINE"
Nephrologist visit	IPDB OHIP	Mainspecialty = "NEPHROLOGY" OR OHIP Feecode: A160, A161, A163-A166, A168, A865, C160-C167, C169, C865, W165, W160-W166, W168, W865, W862, W864, W867, W869,
Orthopedist visit	IPDB	Mainspecialty= "ORTHOPEDIC SURGERY"
Endocrinologist visit	IPDB	Mainspecialty = "ENDOCRINOLOGY"
Internist visit	IPDB	Mainspeciality = "INTERNAL MEDICINE"
Geriatrician visit	IPDB	Mainspecialty = "GERIATRIC MEDICINE"
Ophthalmologist visit	IPDB	Mainspecialty= "OTHALMOLOGY"
episodes of care	CIHI-DAD	ADMDATE, DDATE, EPI, EPIFLAG, EPIVISIT
ER visits	NACRS	"regdate"
Laboratory calcium test	OLIS OHIP	OHIP FEECODE: L045, L046 OBSERVATIONCODE: 29265-6, 1995-0, 19072-8, 1994-3, 47598-8, 34581-9, 59473-9, 41645-3, 12180-6, 13959-2, 47596-2, 53140-0, 41644-6, 53139-2, 3000-9
Laboratory serum creatinine tests	OHIP	OHIP feecode: L065, L067, L068
CT scan	OHIP	OHIP Feecode: X126, X188, X400-X410, X124, X231-X233, X128, X415, X416
Carotid ultrasound	OHIP CIHI-DAD	OHIP Feecode: J201, J501, J190, J490 CCI: 3JE30, 3JG30
Echocardiography	OHIP CIHI-DAD	OHIP Feecode: G560-G562, G566-G568, G570-G572, G574-G578, G581 CCI: 3IP30
Cardiac stress test	OHIP CIHI DAD	OHIP Feecode: G315, G174, G112, G112, G319, G582, G583, G584, J604, J606-J609, J611-J613, J667, J807- J809, J804, J811-J813, J867, J666, J866 CCI: 2HZ08, 3IP70
Bone mineral density test	OHIP	OHIP Feecode: J654, J688, J854, J888, X149, X152, X153, X155, Y654, Y688, Y854, Y888
Chest x-ray	OHIP	OHIP Feecode: X090, X091, X092, X195
Pulmonary function test	OHIP	OHIP Feecode: J301, J303-J311, J313, J315-J320, J322-J324, J327, J328, J330-J335, J340, J341, E450, E451

RPDB: Registered Persons Database, ODB: Ontario Drug Benefit, IPDB: ICES Physician Database, CIHI-DAD: Canadian Institute of Health Information Discharge Abstract Database, OHIP: Ontario Health Insurance Plan, NACRS: National Ambulatory Care Reporting System, OLIS: Ontario Lab Information Services,

Appendix B.D- Drug Identification Numbers used to identify study drugs

Medication	Drug Identification Numbers included
Canagliflozin	2425483, 2425491
Dapagliflozin	2435462, 2435470 With Metformin: 2449935, 2449943
Empagliflozin	2443937, 2443945 With Metformin: 2456575, 2456583, 2456591, 2456605, 2456613, 2456621
Linagliptin	2370921 With Metformin: 2403250, 2403269, 2403277
Sitagliptin	2388839, 2388847, 2303922 With Metformin: 2333856, 2333864, 2333872
Saxagliptin	2403250, 2403269, 2403277 With Metformin: 2389169, 2389177, 2389185

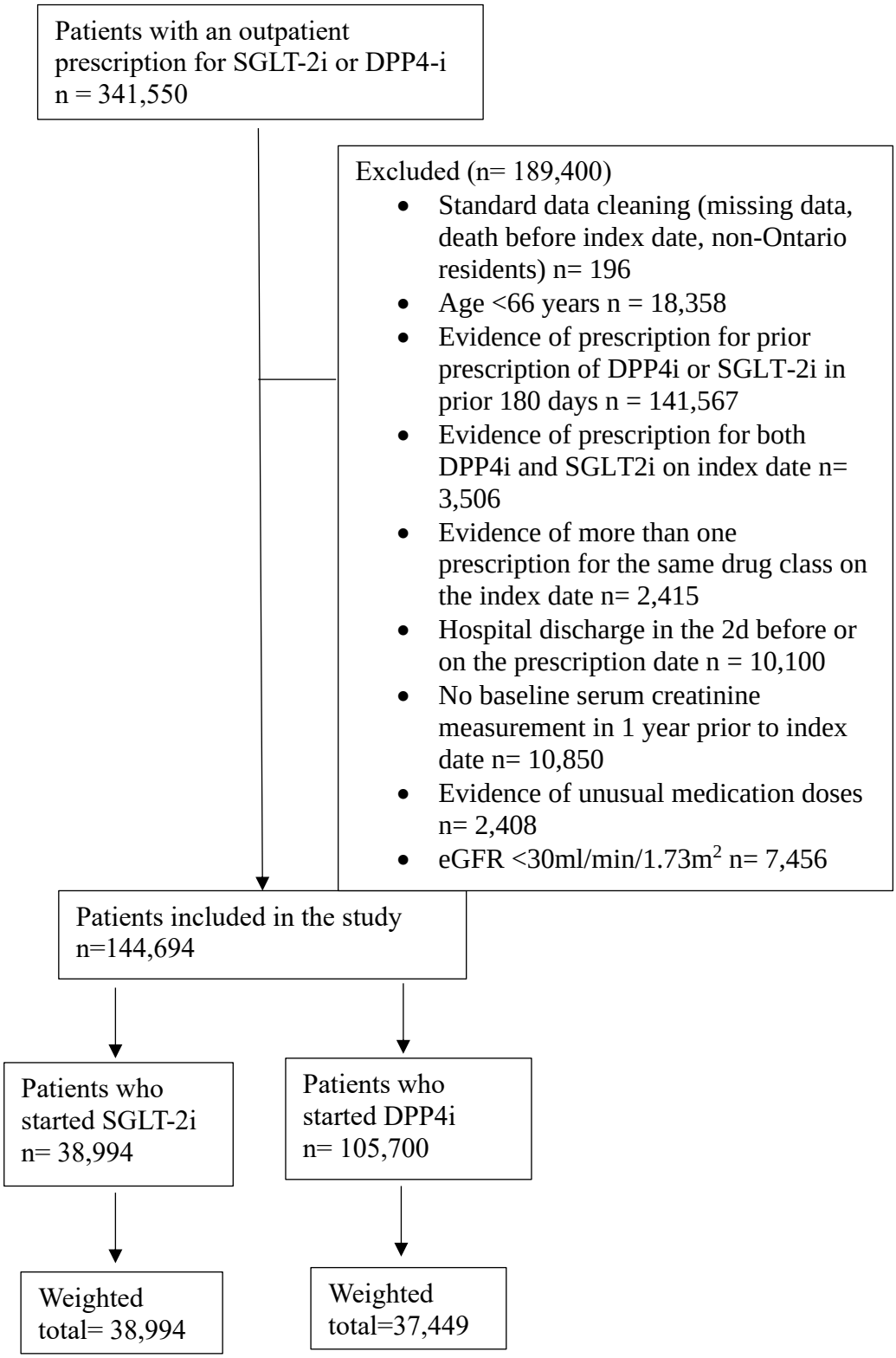
Appendix B.E- Codes used to define study outcomes

Outcome		Database Used	Codes Used
Fracture	Hip	CIHI DAD	ICD10: S720, S721, S722
	Spine	CIHI DAD CIHI NACRS OHIP	S220, S221, S320, S327, S328 OHIP Diagnostic code: 805
	Shoulder and Upper Arm	CIHI DAD, NACRS OHIP	ICD10: S422 OHIP Diagnostic Code: 812
	Wrist and Forearm	CIHI DAD NACRS OHIP	ICD10: S520-S529 OHIP Diagnostic Code: 813
	Pelvic	CIHI DAD NACRS OHIP	S321, S323-S328 OHIP Diagnostic Code: 808
Hypoglycemia		CIHI- DAD NACRS	ICD10: E15, E160, E161, E162, E1063, E1163, E1363, E1463
Falls		CIHI-DAD	ICD10: W00-W19
Hypotension		CIHI-DAD	ICD10: I95

Appendix B.F- Covariates used to create the propensity score

Demographics	Age, Sex, Income quintile, Rurality, Residential status – Long-term care, Prescriber
Comorbidities	Charlson comorbidity index, duration of diabetes, fragility fracture, previous fall, major cancer, dementia, rheumatoid arthritis, osteoporosis, hypertension, hypotension, coronary artery disease, arrhythmia, diabetic retinopathy, diabetic neuropathy, hypoglycemia, peripheral vascular disease, liver disease, COPD CHF, hypothyroidism, disorder of calcium metabolism/dietary calcium deficiency, stroke/TIA, syncope, alcohol misuse
Medication Use	Number of unique drug names, bisphosphonates, denosumab, oral steroid, estrogen, proton pump inhibitors, loop diuretics, potassium-sparing diuretics, thiazide diuretics, beta blockers, opiates, antidepressants, antipsychotics, testosterone, number of unique oral hypoglycemic agents used, Acarbose, gliclazide, glyburide, metformin, thiazolidinedione
Health Care Utilization	Diabetes management, GP/FP visits, nephrologist visit, orthopedist visit, endocrinologist visit, internist visit, geriatrician visit, ophthalmologist visit, number of episodes of care, number of ER visits
Investigations	Hemoglobin A1C, ACR, laboratory calcium testing, laboratory serum creatinine testing, CT scan, carotid ultrasound, echocardiography, cardiac stress test, bone mineral density test, chest x-ray, pulmonary function test

Appendix G- Study flow diagram of older adults with a new prescription for SGLT-2i or DPP-4i



Appendix B.H- Full baseline characteristics for the weighted and unweighted cohorts

	Unweighted (N=144,694)			Weighted (N=76,443)		
Variable	**DPP-4i users (N=105,700)**	**SGLT-2i users (N=38,994)**	**Standardized Difference**	**DPP-4i users (N=37,449)**	**SGLT-2i users (N=38,994)**	**Standardized Difference**
Demographics						
Age, mean, y (SD)	74 (7)	72 (5)	0.38	72 (3)	72 (5)	0.00
Female No. (%)	49,289 (47)	15,457 (40)	0.14	15,258 (41)	15,457 (40)	0.02
Income Quintile No. (%)						
1	24,747 (23)	8,257 (21)	0.05	8,062 (22)	8,257 (21)	0.01
2	23,603 (22)	8,383 (22)	0.02	8,042 (22)	8,383 (22)	0.00
3	21,946 (21)	8,109 (21)	0.00	7,815 (21)	8,109 (21)	0.00
4	18,758 (18)	7,405 (19)	0.03	7,033 (19)	7,405 (19)	0.01
5	16,646 (16)	6,840 (18)	0.05	6,497 (17)	6,840 (18)	0.00
Rurality No. (%)	10,947 (10)	6,167 (16)	0.16	5,935 (16)	6,167 (16)	0.00
Index year						
2015	14,152 (13)	3,770 (10)	0.12	3,698 (10)	3,770 (10)	0.01
2016	28,596 (27)	6,804 (17)	0.23	6,679 (18)	6,804 (17)	0.01
2017	24,459 (23)	8,996 (23)	0.00	8,575 (23)	8,996 (23)	0.00
2018	22,869 (22)	9,886 (25)	0.09	9,421 (25)	9,886 (25)	0.00
2019	15,624 (15)	9,538 (25)	0.25	9,074 (24)	9,538 (25)	0.01
Long-term care status No. (%)	3,560 (3)	283 (1)	0.19	302 (1)	283 (1)	0.01
Prescriber, No. (%)						
Cardiology	440 (0)	1580 (4)	0.25	636 (2)	1,580 (4)	0.14
Endocrinology	8,743 (8)	5,480 (14)	0.18	5,068 (14)	5,480 (14)	0.02
General Practitioner	85,858 (81)	26,190 (6)	0.32	26,398 (71)	26,190 (67)	0.07
Internal Medicine	3,579 (3)	2652 (7)	0.16	2,421 (7)	2652 (7)	0.01

Nephrology	803 (1)	758 (2)	0.10	612 (2)	758 (2)	0.02
Other	6,277 (6)	2,334 (6)	0.00	2,313 (6)	2,334 (6)	0.01
Comorbidities, No. (%)						
Mean Charlson comorbidity index (SD)	0.5 (1.2)	0.4 (1.1)	0.05	0.4 (0.7)	0.4 (1.1)	0.02
Mean duration of diabetes, y (SD)	11.5 (7.4)	12.4 (7.6)	0.11	12.2 (4.4)	12.4 (7.6)	0.03
Fragility fracture	4,012 (4)	1,204 (3)	0.04	1,197 (3)	1,204 (3)	0.01
Previous fall	17,225 (16)	5,572 (14)	0.06	5,439 (15)	5,572 (14)	0.01
Major cancer	13,220 (13)	4,290 (11)	0.05	4,153 (11)	4,290 (11)	0.00
Dementia	7,636 (7)	1,094 (3)	0.20	1,111 (3)	1,094 (3)	0.01
Rheumatoid arthritis	2,398 (2)	848 (2)	0.01	815 (2)	848 (2)	0.00
Osteoporosis	7,839 (7)	1,969 (5)	0.10	1,926 (5)	1,969 (5)	0.00
Hypertension	85,593 (81)	31,941 (82)	0.02	30,500 (81)	31,941 (82)	0.01
Hypotension	1,802 (2)	497 (1)	0.03	472 (1)	497 (1)	0.00
Coronary artery disease (excluding angina)	24,571 (23)	12,258 (31)	0.18	10,961 (29)	12,258 (31)	0.05
Arrhythmia	8,612 (8)	3,355 (9)	0.02	3,047 (8)	3,355 (9)	0.02
Diabetic retinopathy	750 (1)	338 (1)	0.02	314 (1)	338 (1)	0.01
Diabetic neuropathy	1,431 (1)	604 (2)	0.01	577 (2)	604 (2)	0.00
Hypoglycemia	2,387 (2)	805 (2)	0.01	756 (2)	805 (2)	0.01
Peripheral vascular disease	1,196 (1)	487 (1)	0.01	436 (1)	487 (1)	0.00
Liver disease	5,014 (5)	1,940 (5)	0.01	1,862 (5)	1,940 (5)	0.00
Coronary obstructive pulmonary disease	21,795 (21)	8,718 (22)	0.04	8,386 (22)	8,718 (22)	0.00
Congestive heart failure	12,300 (12)	5,093 (13)	0.05	4,607 (12)	5,093 (13)	0.02
Hypothyroidism	1,265 (1)	338 (1)	0.03	330 (1)	338 (1)	0.00
Disorder of calcium metabolism/dietary calcium deficiency	379 (0)	65 (0)	0.04	67 (0)	65 (0)	0.00
Stroke/TIA	10,153 (10)	3,089 (8)	0.06	2,935 (8)	3,089 (8)	0.00

Syncope	1,324 (1)	383 (1)	0.03	377 (1)	383 (1)	0.00
Alcohol misuse	624 (1)	234 (1)	0.00	223 (1)	234 (1)	0.00
Medication Use, No. (%)						
Mean number of Unique Drug Names (SD)	6.9 (4.5)	7.6 (4.2)	0.18	7.6 (2.7)	7.6 (4.2)	0.02
Bisphosphonates	9,199 (9)	1,952 (5)	0.15	1,939 (5)	1,952 (5)	0.01
Denosumab	2,053 (2)	486 (1)	0.06	479 (1)	486 (1)	0.01
Oral steroid	8,038 (8)	2,732 (7)	0.02	2,641 (7)	2,732 (7)	0.00
Estrogen	2,099 (2)	802 (2)	0.01	814 (2)	802 (2)	0.01
Thiazolidinedione	466 (0)	144 (0)	0.00	146 (0)	144 (0)	0.00
Proton pump inhibitors	28,426 (27)	11,396 (29)	0.05	10,895 (29)	11,396 (29)	0.00
Loop diuretics	9,830 (9)	4,049 (10)	0.04	3,701 (10)	4,049 (10)	0.02
Potassium-sparing diuretics	3,673 (4)	1,872 (5)	0.07	1671 (5)	1,872 (5)	0.01
Thiazide diuretics	13,960 (13)	6,183 (16)	0.08	5,935 (16)	6,183 (16)	0.00
Beta blockers	28,903 (27)	13,662 (35)	0.17	12,554 (34)	13,662 (35)	0.03
Opiates	11,846 (11)	4,571 (12)	0.02	4,434 (12)	4,571 (12)	0.00
Antidepressants	17,489 (17)	6,965 (18)	0.04	6,758 (18)	6,965 (18)	0.00
Antipsychotics	3,285 (3)	874 (2)	0.06	890 (2)	874 (2)	0.01
Testosterone	352 (0)	216 (1)	0.04	204 (1)	216 (1)	0.01
Number of unique oral hypoglycemic agents used						
0	37,006 (35)	10,916 (28)	0.15	10,454 (28)	10,916 (28)	0.00
1	51,484 (49)	20,902 (54)	0.10	19,976 (53)	20,902 (54)	0.01
2+	17,210 (16)	7,176 (18)	0.06	7,019 (19)	7,176 (18)	0.01
Acarbose	502 (1)	218 (1)	0.01	210 (1)	218 (1)	0.00
Gliclazide	20,070 (19)	8,082 (21)	0.04	7,927 (21)	8,082 (21)	0.01
Glyburide	3,905 (4)	1,105 (3)	0.05	1,115 (3)	1,105 (3)	0.01

Metformin	61,485 (58)	25,896 (66)	0.17	24,803 (66)	25,896 (66)	0.00
Health care utilization, No. (%)						
General practitioner visits	103,120 (98)	37,951 (97)	0.02	36,397 (97)	37,951 (97)	0.01
Mean number of visits (SD)	14.2 (19.2)	12.4 (15.0)	0.11	12.4 (8.2)	12.4 (15.0)	0.01
Nephrologist visit	7,743 (7)	2,426 (6)	0.04	2,216 (6)	2,426 (6)	0.01
Mean number of visits (SD)	0.18 (1.2)	0.13 (0.7)	0.05	0.13 (0.52)	0.13 (0.7)	0.00
Orthopedist visit	10,378 (10)	4,060 (10)	0.02	3,944 (11)	4,060 (10)	0.00
Mean number of visits (SD)	0.5 (3.1)	0.5 (2.5)	0.01	0.5 (1.8)	0.5 (2.5)	0.01
Endocrinologist visit	12,998 (12)	7,112 (18)	0.16	6,499 (17)	7,112 (18)	0.02
Mean number of visits (SD)	0.5 (2.0)	0.8 (2.2)	0.13	0.7 (1.2)	0.8 (2.2)	0.06
Internist visit	31,277 (30)	11,993 (31)	0.03	11,386 (30)	11,993 (31)	0.01
Mean number of visits (SD)	2.3 (8.02)	1.9 (5.5)	0.05	2.0 (3.74)	1.9 (5.5)	0.02
Geriatrician visit	3,980 (4)	759 (2)	0.11	732 (2)	759 (2)	0.01
Mean number of visits (SD)	0.2 (2.4)	0.1 (1.1)	0.08	0.1 (0.8)	0.1 (1.1)	0.01
Ophthalmologist visit	32,083 (30)	12,550 (32)	0.04	11,957 (32)	12,550 (32)	0.01
Mean number of visits (SD)	2.2 (5.9)	2.53 (6.6)	0.05	2.46 (3.8)	2.53 (6.6)	0.01
Episodes of care	15,087 (14)	4,770 (12)	0.06	4,455 (12)	4,770 (12)	0.01
Mean number of visits (SD)	0.2 (0.58)	0.16 (0.49)	0.07	0.16 (0.3)	0.16 (0.49)	0.00
Emergency Room visits	35,140 (33)	12,514 (32)	0.02	11,961 (32)	12,514 (32)	0.00
Mean number of visits (SD)	0.7 (1.4)	0.6 (1.3)	0.04	0.6 (0.8)	0.6 (1.3)	0.02
Laboratory Testing No. (%)						
Diabetes management	54,022 (51)	22,108 (57)	0.11	21,383 (57)	22,108 (57)	0.01
Mean Hemoglobin A1c (SD)	8.1 (1.6)	8.0 (1.5)	0.03	8.1 (0.9)	8.0 (1.5)	0.02
Missing Hemoglobin A1c	3,097 (3)	702 (2)	0.07	844 (2)	702 (2)	0.04
Mean Urine Albumin to Creatinine ratio (SD)	11.6 (42.2)	11.8 (41.4)	0.01	11.3 (25.8)	11.8 (41.4)	0.02

Missing Urine Albumin to Creatinine ratio	31,502 (30)	9,683 (25)	0.11	9,370 (25)	9,683 (25)	0.00
Mean number of laboratory serum creatinine tests (SD)	4.1 (5.6)	3.8 (4.0)	0.06	3.8 (2.5)	3.8 (4.0)	0.01
Mean eGFR (SD)	69 (19)	73 (17)	0.23	73 (10)	73 (17)	0.01
eGFR						
≥90	14,853 (14)	6,485 (17)	0.07	6,319 (17)	6,485 (17)	0.01
60-<90	55,500 (53)	23,520 (60)	0.16	22,547 (60)	23,520 (60)	0.00
45-<60	20,617 (20)	6,577 (17)	0.07	6,250 (17)	6,577 (17)	0.01
30-<45	14,730 (14)	2,412 (6)	0.26	2,332 (6)	2,412 (6)	0.00
Laboratory calcium test	26,012 (25)	7,798 (20)	0.11	7,414 (20)	7,798 (20)	0.01
Mean number of tests (SD)	0.6 (1.9)	0.4 (1.4)	0.11	0.4 (0.9)	0.4 (1.4)	0.03
Diagnostic Imaging No. (%)						
CT scan	22,582 (21)	7,271 (19)	0.07	6,952 (19)	7,271 (19)	0.00
Carotid ultrasound	4,598 (4)	1,789 (5)	0.01	1,656 (4)	1,789 (5)	0.01
Echocardiography	21,789 (21)	9,545 (25)	0.09	8,573 (23)	9,545 (25)	0.04
Cardiac stress test	12,626 (12)	6,419 (17)	0.13	5,753 (15)	6,419 (17)	0.03
Bone mineral density test	6,743 (6)	2,109 (5)	0.04	2,062 (6)	2,109 (5)	0.00
Chest x-ray	32,516 (31)	11,218 (29)	0.04	10,593 (28)	11,218 (29)	0.01
Pulmonary function test	7,451 (7)	3,504 (9)	0.07	3,221 (9)	3,504 (9)	0.01

Abbreviations: DPP-4i- Dipeptidyl peptidase 4 inhibitor, SGLT-2i- Sodium glucose 2 transporter inhibitor, SD: standard deviation, TIA- Transient ischemic attack, Charlson comorbidity score was calculated using five years of hospitalization data. “No hospitalizations” received a score of 0.

B.I – Full baseline characteristics, stratified by eGFR category, after weighting

	eGFR ≥90 (N=12,814)			eGFR 60 - <90 (N=46,145)			eGFR 45 - <60 (N=12,777)			eGFR 30 - <45 (N=4,617)		
	DPP4i users (N=6,329)	**SGLT2i users (N=6,485)**	Std Diff	**DPP4i users (N=22,625)**	**SGLT2i users (N=23,520)**	Std Diff	**DPP4i users (N=6,200)**	**SGLT2i users (N=6,577)**	Std Diff	**DPP4i users (N=2,205)**	**SGLT2i users (N=2,412)**	Std Diff
Demographics												
Age, mean, y (SD)	69 (2)	69 (3)	0.00	72 (3)	72 (5)	0.01	74 (3)	74 (6)	0.00	76 (3)	76 (6)	0.02
Female No. (%)	2,744 (43)	2,745 (42)	0.02	8,878 (39)	8,964 (38)	0.02	2,594 (42)	2,659 (40)	0.03	1,020 (46)	1,089 (45)	0.02
Income quintile No. (%)												
1	1,413 (22)	1,410 (22)	0.01	4,799 (21)	4,926 (21)	0.01	1,329 (21)	1,372 (21)	0.01	511 (23)	549 (23)	0.01
2	1,381 (22)	1,417 (22)	0.00	4,818 (21)	5,024 (21)	0.00	1,335 (22)	1,414 (22)	0.00	485 (22)	528 (22)	0.00
3	1,295 (21)	1,336 (21)	0.00	4,790 (21)	4,947 (21)	0.00	1,264 (20)	1,341 (20)	0.00	450 (20)	485 (20)	0.01
4	1,185 (19)	1,224 (19)	0.01	4,225 (19)	4,441 (19)	0.01	1,184 (19)	1,275 (19)	0.01	408 (19)	465 (19)	0.02
5	1,057 (17)	1,098 (17)	0.01	3,992 (18)	4,182 (18)	0.01	1,086 (18)	1,175 (18)	0.01	352 (16)	385 (16)	0.00
Rurality No. (%)	1,136 (18)	1,177 (18)	0.01	3,545 (16)	3,655 (16)	0.01	925 (15)	975 (15)	0.00	331 (15)	360 (15)	0.00
Index year No. (%)												
2015	753 (12)	785 (12)	0.01	2,266 (10)	2,300 (10)	0.01	545 (9)	543 (8)	0.02	144 (7)	142 (6)	0.02

2016	1,437 (23)	1,457 (23)	0.00	4,101 (18)	4,157 (18)	0.01	913 (15)	934 (14)	0.01	254 (12)	256 (11)	0.03
2017	1,366 (22)	1,396 (22)	0.00	5,456 (24)	5,712 (24)	0.00	1,389 (22)	1,468 (22)	0.00	404 (18)	420 (17)	0.02
2018	1,434 (23)	1,482 (23)	0.00	5,737 (25)	6,003 (26)	0.00	1,667 (27)	1,783 (27)	0.00	579 (26)	618 (26)	0.02
2019	1,339 (21)	1,365 (21)	0.00	5,065 (22)	5,348 (23)	0.01	1,684 (27)	1,849 (28)	0.02	824 (37)	976 (41)	0.07
Long-term care status No. (%)	42 (1)	37 (1)	0.01	167 (1)	154 (1)	0.00	64 (1)	60 (1)	0.01	33 (2)	32 (1)	0.02
Prescriber No. (%)												
Cardiology	79 (1)	140 (2)	0.07	366 (2)	931 (4)	0.15	128 (2%)	362 (6)	0.18	55 (3)	147 (6)	0.18
Endocrinology	831 (13)	893 (14)	0.02	3,074 (14)	3,333 (14)	0.02	902 (15)	957 (15)	0.00	282 (13)	297 (12)	0.02
General Practitioner	4,603 (73)	4,597 (71)	0.04	16,323 (72)	16,216 (69)	0.07	4,136 (67)	4,097 (62)	0.09	1,295 (59)	1,280 (53)	0.11
Internal Medicine	337 (5)	361 (6)	0.01	1342 (6)	1476 (6)	0.02	514 (8)	576 (9)	0.02	218 (10)	239 (10)	0.00
Nephrology	25 (%)	38 (1)	0.03	127 (1)	168 (1)	0.01	173 (3)	235 (4)	0.05	226 (10)	317 (13)	0.09
Other	455 (7)	456 (7)	0.01	1394 (6)	1,396 (6)	0.01	344 (6)	350 (5)	0.01	130 (6)	132 (6)	0.02
Comorbidities No. (%)												
Mean Charlson comorbidity index (SD)	0.3 (0.7)	0.4 (1.0)	0.01	0.4 (0.7)	0.4 (1.0)	0.02	0.6 (0.7)	0.6 (1.2)	0.02	0.8 (0.6)	0.8 (1.4)	0.00

Mean duration of diabetes, y (SD)	11.2 (4.6)	11.4 (7.2)	0.02	11.9 (4.7)	12.1 (7.5)	0.03	13.4 (4.2)	13.5 (7.9)	0.02	15.1 (3.0)	15.3 (7.9)	0.03
Fragility fracture	207 (3)	206 (3)	0.01	672 (3)	678 (3)	0.01	228 (4)	228 (4)	0.01	85 (4)	92 (4)	0.01
Previous fall	885 (14)	907 (14)	0.00	3,139 (14)	3,207 (14)	0.01	1,000 (16)	1,029 (16)	0.01	397 (18)	429 (18)	0.01
Major cancer	619 (10)	642 (10)	0.00	2,520 (11)	2584 (11)	0.00	714 (12)	744 (11)	0.01	296 (13)	320 (13)	0.00
Dementia	94 (2)	90 (1)	0.01	653 (3)	635 (3)	0.01	258 (4)	255 (4)	0.02	108 (5)	114 (5)	0.01
Rheumatoid arthritis	145 (2)	150 (2)	0.00	469 (2)	489 (2)	0.00	147 (2)	151 (2)	0.01	52 (2)	58 (2)	0.00
Osteoporosis	334 (5)	338 (5)	0.00	1,178 (5)	1,189 (5)	0.00	307 (5)	321 (5)	0.00	112 (5)	121 (5)	0.00
Hypertension	4,728 (75)	4,859 (75)	0.00	18,237 (81)	19,058 (81)	0.01	5,422 (88)	5,783 (88)	0.01	2,035 (92)	2,241 (93)	0.03
Hypotension	47 (1)	50 (1)	0.01	233 (1)	236 (1)	0.00	122 (2)	144 (2)	0.01	66 (3)	67 (3)	0.01
Coronary artery disease (excluding angina)	1,376 (22)	1,512 (23)	0.04	6,543 (29)	7,317 (31)	0.05	2,151 (35)	2,445 (37)	0.05	853 (39)	984 (41)	0.04
Arrhythmia	292 (5)	310 (5)	0.01	1,664 (7)	1,831 (8)	0.02	736 (12)	829 (13)	0.02	334 (15)	385 (16)	0.02
Diabetic retinopathy	34 (1)	36 (1)	0.01	174 (1)	181 (1)	0.00	67 (1)	77 (1)	0.01	37 (2)	44 (2)	0.01
Diabetic neuropathy	79 (1)	82 (1)	0.01	310 (1)	325 (1)	0.00	125 (2)	141 (2)	0.01	55 (3)	56 (2)	0.01
Hypoglycemia	89 (1)	90 (1)	0.00	367 (2)	392 (2)	0.01	197 (3)	213 (3)	0.00	104 (5)	110 (5)	0.00

Peripheral vascular disease	57 (1)	66 (1)	0.01	243 (1)	279 (1)	0.01	87 (1)	96 (2)	0.01	45 (2)	46 (2)	0.01
Liver disease	386 (6)	391 (6)	0.00	1,069 (5)	1113 (5)	0.00	276 (4)	300 (5)	0.01	120 (5)	136 (6)	0.01
Coronary Obstructive Pulmonary Disease	1,358 (21)	1,373 (21)	0.00	4,908 (22)	5,081 (22)	0.00	1,539 (25)	1,633 (25)	0.00	577 (26)	631 (26)	0.00
Congestive Heart Failure	406 (6)	430 (7)	0.01	2404 (11)	2,659 (11)	0.02	1,164 (19)	1,315 (20)	0.03	592 (27)	689 (29)	0.04
Hypothyroidism	38 (1)	36 (1)	0.00	189 (1)	194 (1)	0.00	64 (1)	68 (1)	0.00	36 (2)	40 (2)	0.01
Calcium Deficiency	<6 (0)	<6 (0)		>42 (0)	>40 (0)		9 (0)	9 (0)	0.00	9 (0)	10 (0)	0.00
Stroke/TIA	360 (6)	374 (6)	0.00	1,714 (8)	1,812 (8)	0.00	632 (10)	659 (10)	0.01	230 (10)	244 (10)	0.01
Syncope	38 (1)	36 (1)	0.00	206 (1)	208 (1)	0.00	82 (1)	90 (1)	0.01	46 (2)	49 (2)	0.01
Alcohol misuse	44 (1)	46 (1)	0.00	109 (1)	116 (1)	0.00	48 (1)	52 (1)	0.00	17 (1)	20 (1)	0.00
Medication Use, No. (%)												
Mean number of Unique Drug Names	6.8 (2.9)	6.8 (3.9)	0.00	7.4 (2.8)	7.4 (4.1)	0.01	8.5 (2.6)	8.6 (4.3)	0.02	9.3 (1.8)	9.4 (4.4)	0.04
Bisphosphonates	321 (5)	322 (5)	0.00	1,152 (5)	1,146 (5)	0.01	341 (6)	345 (5)	0.01	128 (6)	139 (6)	0.00
Denosumab	76 (1)	72 (1)	0.01	283 (1)	286 (1)	0.00	85 (1)	85 (1)	0.01	37 (2)	43 (2)	0.01

Oral steroid	397 (6)	401 (6)	0.00	1,555 (7)	1,588 (7)	0.00	510 (8)	535 (8)	0.00	191 (9)	208 (9)	0.00
Estrogen	161 (3)	163 (3)	0.00	498 (2)	481 (2)	0.01	124 (2)	118 (2)	0.01	36 (2)	40 (2)	0.01
Thiazolidinedione	24 (0)	21 (0)	0.02	83 (0)	83 (0)	0.00	34 (1)	32 (1)	0.01	8 (0)	8 (0)	0.02
Proton pump inhibitors	1,492 (24)	1,525 (24)	0.00	6,361 (28)	6,645 (28)	0.00	2,167 (35)	2,303 (35)	0.00	836 (38)	923 (38)	0.01
Loop diuretics	324 (5)	327 (5)	0.00	1,801 (8)	1,982 (8)	0.01	986 (16)	1,101 (17)	0.02	562 (26)	639 (27)	0.02
Potassium-sparing diuretics	114 (2)	129 (2)	0.01	851 (4)	950 (4)	0.01	469 (8)	537 (8)	0.02	210 (10)	256 (11)	0.04
Thiazide diuretics	857 (14)	874 (14)	0.00	3437 (15)	3563 (15)	0.00	1,178 (19)	1,244 (19)	0.00	446 (20)	502 (21)	0.01
Beta blockers	1,550 (25)	1,650 (25)	0.02	7,302 (32)	7,930 (34)	0.03	2,574 (42)	2,854 (43)	0.04	1,077 (49)	1,228 (51)	0.04
Opiates	802 (13)	811 (13)	0.01	2,561 (11)	2,631 (11)	0.00	746 (12)	781 (12)	0.00	321 (15)	348 (14)	0.01
Antidepressants	1,113 (18)	1,122 (17)	0.01	3,922 (17)	4,032 (17)	0.01	1,249 (20)	1297 (20)	0.01	469 (21)	514 (21)	0.00
Antipsychotics	168 (3)	153 (2)	0.01	503 (2)	496 (2)	0.01	170 (3)	171 (3%)	0.01	51 (2)	54 (2)	0.01
Testosterone	27 (0)	30 (1)	0.01	127 (1)	129 (1)	0.01	35 (1)	40 (1)	0.00	14 (1)	17 (1)	0.01
Number of unique oral hypoglycemic agents used												
0	1,622 (26)	1,661 (26)	0.00	6,199 (27)	6,472 (28)	0.00	1,785 (29)	1,909 (29)	0.00	790 (36)	874 (36)	0.01

1	3,407 (54)	3,528 (54)	0.01	12,187 (54)	12,729 (54)	0.00	3,281 (53)	3,490 (53)	0.00	1,058 (48)	1,155 (48)	0.00
2+	1,301 (21)	1,296 (20)	0.01	4,239 (19)	4,319 (18)	0.01	1,132 (18)	1,178 (18)	0.01	358 (16)	383 (16)	0.01
Acarbose	31 (1)	29 (0)	0.01	131 (1)	138 (1)	0.00	35 (1)	36 (1)	0.01	15 (1)	15 (1)	0.01
Gliclazide	1,377 (22)	1,383 (21)	0.01	4,771 (21)	4,837 (21)	0.01	1,340 (22)	1,373 (21)	0.02	458 (21)	489 (20)	0.01
Glyburide	202 (3)	198 (3)	0.01	652 (3)	641 (3)	0.01	207 (3)	207 (3)	0.01	59 (3)	59 (2)	0.02
Metformin	4,406 (70)	4,516 (70)	0.00	15,143 (67)	15,783 (67)	0.00	3,963 (64)	4,233 (64)	0.01	1,248 (57)	1,364 (57)	0.00
Health Care Utilization, No. (%)												
General Practitioner visits	6,129 (97)	6,297 (97)	0.02	21,997 (97)	22,883 (97)	0.01	6,034 (97)	6,429 (98)	0.02	2,151 (98)	2,342 (97)	0.02
Mean number of visits (SD)	11.9 (8.4)	11.6 (15.7)	0.02	12.1 (8.5)	12.1 (14.3)	0.01	13.4 (8.4)	13.4 (15.9)	0.00	14.5 (6.2)	14.4 (15.9)	0.01
Nephrologist visit	154 (2)	178 (3)	0.02	703 (3)	759 (3)	0.01	662 (11)	738 (11)	0.02	637 (29)	751 (31)	0.05
Mean number of visits (SD)	0.0 (0.3)	0.1 (0.4)	0.03	0.1 (0.4)	0.1 (0.5)	0.00	0.2 (0.7)	0.2 (0.9)	0.03	0.7 (0.9)	0.7 (1.5)	0.03
Orthopedist visit	689 (11)	689 (11)	0.01	2,332 (10)	2,392 (10)	0.00	669 (11)	711 (11)	0.00	238 (11)	268 (11)	0.01
Mean number of visits (SD)	0.6 (2.3)	0.5 (2.3)	0.03	0.5 (1.6)	0.5 (2.6)	0.01	0.5 (2.2)	0.5 (2.3)	0.01	0.6 (1.0)	0.5 (2.1)	0.03

Endocrinol ogist visit	1,035 (16)	1,117 (17)	0.02	3,844 (17)	4,201 (18)	0.02	1,206 (20)	1,317 (20)	0.01	419 (19)	477 (20)	0.02
Mean number of visits (SD)	0.6 (1.2)	0.8 (2.2)	0.07	0.7 (1.3)	0.8 (2.1)	0.05	0.8 (1.2)	0.9 (2.4)	0.04	0.8 (1.0)	1.0 (2.5)	0.08
Internist visit	1,698 (27)	1,760 (27)	0.01	6,640 (29)	6,962 (30)	0.01	2,155 (35)	2,329 (35)	0.01	866 (39)	942 (39)	0.00
Mean number of visits (SD)	1.6 (4.0)	1.5 (4.3)	0.02	1.9 (3.8)	1.7 (5.4)	0.03	2.5 (4.4)	2.4 (6.2)	0.02	3.3 (3.7)	2.9 (6.8)	0.08
Geriatrician visit	78 (1)	79 (1)	0.00	424 (2)	437 (2)	0.00	157 (3)	166 (3)	0.00	71 (3)	77 (3)	0.00
Mean number of visits (SD)	0.1 (0.6)	0.1 (1.0)	0.00	0.1 (0.9)	0.1 (1.0)	0.01	0.1 (0.8)	0.1 (1.1)	0.02	0.2 (0.7)	0.2 (1.7)	0.01
Ophthalmol ogist visit	1,755 (28)	1,811 (28)	0.00	7,154 (32)	7,500 (32)	0.01	2,133 (34)	2,284 (35)	0.01	864 (39)	955 (40)	0.01
Mean number of visits (SD)	2.0 (3.6)	2.0 (5.7)	0.00	2.4 (4.1)	2.5 (6.4)	0.01	2.7 (3.7)	2.9 (7.2)	0.04	3.3 (2.8)	3.6 (8.6)	0.05
Episodes of care	689 (11)	716 (11)	0.00	2462 (11)	2629 (11)	0.01	883 (14)	977 (15)	0.02	415 (19)	448 (19)	0.01
Mean number of visits (SD)	0.1 (0.3)	0.1 (0.4)	0.00	0.1 (0.3)	0.1 (0.5)	0.00	0.2 (0.3)	0.2 (0.6)	0.02	0.3 (0.3)	0.3 (0.7)	0.02
Emergency room visits	1,911 (30)	1,979 (31)	0.01	6,907 (31)	7,201 (31)	0.00	2,199 (36)	2,341 (36)	0.00	920 (42)	993 (41)	0.01

Mean number of visits (SD)	0.6 (0.92)	0.56 (1.18)	0.04	0.59 (0.88)	0.57 (1.27)	0.02	0.74 (0.83)	0.71 (1.39)	0.03	0.89 (0.61)	0.86 (1.63)	0.02
Laboratory Testing No. (%)												
Diabetes management	3,594 (57)	3,645 (56)	0.01	13,056 (58)	13,480 (57)	0.01	3,505 (57)	3,699 (56)	0.01	1,192 (54)	1,284 (53)	0.02
Mean Hemoglobin A1C (SD)	8.3 (1.1)	8.3 (1.6)	0.01	8.0 (0.9)	8.0 (1.4)	0.02	8.0 (0.8)	7.9 (1.4)	0.04	8.0 (0.6)	7.9 (1.5)	0.05
Missing Hemoglobin A1C	158 (3)	111 (2)	0.06	492 (2)	386 (2)	0.04	137 (2)	133 (2)	0.01	52 (2)	72 (3)	0.04
Mean Urine albumin to creatinine ratio (SD)	7.5 (19.4)	7.8 (26.4)	0.01	8.3 (20.5)	8.7 (32.5)	0.02	16.5 (30.4)	17.9 (53.1)	0.04	33.5 (34.8)	35.4 (82.6)	0.04
Missing Urine albumin to creatinine ratio	1,620 (26)	1,633 (25)	0.01	5,669 (25)	5,879 (25)	0.00	1,545 (25)	1,633 (25)	0.00	516 (23)	538 (22)	0.03
Laboratory calcium test	1,013 (16)	1,019 (16)	0.01	3,928 (17)	4,107 (18)	0.00	1,548 (25)	1,680 (26)	0.01	873 (40)	992 (41)	0.03
Mean number of calcium tests (SD)	0.3 (1.1)	0.3 (1.4)	0.04	0.4 (1.0)	0.3 (1.2)	0.04	0.6 (1.0)	0.5 (1.8)	0.04	0.9 (0.8)	0.9 (1.7)	0.02

Mean number of laboratory serum creatinine tests (SD)	3.3 (2.8)	3.3 (3.5)	0.01	3.6 (2.6)	3.56 (3.47)	0.00	4.5 (3.0)	4.5 (5.0)	0.01	5.9 (2.7)	5.7 (5.7)	0.05
Mean eGFR (SD)	94 (3)	94 (4)	0.00	76 (6)	76 (9)	0.01	53 (2)	53 (4)	0.00	39 (2)	39 (4)	0.01
Diagnostic Testing No. (%)												
CT scan	1,046 (17)	1,076 (17)	0.00	4,021 (18)	4,186 (18)	0.00	1,336 (22)	1,433 (22)	0.00	534 (24)	576 (24)	0.01
Carotid ultrasound	222 (4)	232 (4)	0.01	983 (4)	1,062 (5)	0.01	317 (5)	352 (5)	0.01	136 (6)	143 (6)	0.01
Echocardiogram	1,153 (18)	1,250 (19)	0.03	4,908 (22)	5,462 (23)	0.04	1,755 (28)	1,999 (30)	0.05	708 (32)	834 (35)	0.05
Cardiac stress test	869 (14)	944 (15)	0.03	3,459 (15)	3,846 (16)	0.03	1,052 (17)	1,200 (18)	0.03	352 (16)	429 (18)	0.05
Bone mineral density test	366 (6)	370 (6)	0.00	1,251 (6)	1262 (5)	0.00	334 (5)	357 (5)	0.00	113 (5)	120 (5)	0.00
Chest x-ray	1,598 (25)	1,656 (26)	0.00	6,165 (27)	6,498 (28)	0.01	1,986 (32)	2,153 (33)	0.01	827 (38)	911 (38)	0.01
Pulmonary function test	467 (7)	488 (8)	0.00	1900 (8)	2050 (9)	0.01	644 (10)	715 (11)	0.02	212 (10)	251 (10)	0.03

Abbreviations: DPP-4i- Dipeptidyl peptidase 4 inhibitor, SGLT-2i- Sodium glucose 2 transporter inhibitor, Std Diff- standardized difference, SD: standard deviation, TIA- Transient ischemic attack, Charlson comorbidity score was calculated using five years of hospitalization data. “No hospitalizations” received a score of 0.

Appendix B.J- Fracture at 180 days by fracture site

Site of Fracture	DPP-4i Users N=37,449 n (%)	SGLT-2i Users N=3,8994 n (%)	HR (95% CI)
Hip	36 (0.1%)	30 (0.08%)	0.81 (0.52-1.24)
Spine	13 (0.03%)	11 (0.03%)	0.83 (0.39-1.78)
Shoulder and Upper Arm	47 (0.12%)	56 (0.14%)	1.15 (0.82-1.63)
Wrist and Forearm	59 (0.16%)	57 (0.15%)	0.92 (0.67-1.27)
Pelvis	32 (0.09%)	24 (0.06%)	0.72 (0.44-1.17)

Appendix C

Supplementary Material for "Hypocalcemia risk of denosumab across the spectrum of kidney disease: A population-based cohort study"

Appendix C.A- The RECORD statement for pharmacoepidemiology (RECORD-PE) checklist of items, extended from the STROBE and RECORD statements, which should be reported in non-interventional pharmacoepidemiological studies using routinely collected health data

Item No	STROBE items	RECORD items	RECORD-PE items	Page No
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 geographical region and timeframe 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 Pg 1/2
Introduction				
Background rationale				
2	Explain the scientific background and rationale for the investigation being reported.	—	—	Introduction Pg 3/4
Objectives				
3	State specific objectives, including any prespecified hypotheses.	—	—	Pg 3
Methods				
Study design				
4	Present key elements of study design early in the paper.	—	4.a: Include details of the specific study design (and its features) and report the use of multiple designs if used.	Pg 3 Appendix E

			4.b: The use of a diagram(s) is recommended to illustrate key aspects of the study design(s), including exposure, washout, lag and observation periods, and covariate definitions as relevant.	
Setting				
5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection.	—	—	Pg 3
Participants				
6	(a) Cohort study—give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. Case-control study—give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls. Cross sectional study—give the eligibility criteria, and the sources and methods of selection of participants. (b) Cohort study—for matched studies, give matching criteria and number of exposed and unexposed. Case-control study—for matched studies, give matching criteria and the number of controls per case.	6.1: The methods of study population selection (such as codes or algorithms used to identify participants) 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.	6.1.a: Describe the study entry criteria and the order in which these criteria were applied to identify the study population. Specify whether only users with a specific indication were included and whether patients were allowed to enter the study population once or if multiple entries were permitted. See explanatory document for guidance related to matched designs.	Pg 4
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.	7.1.a: Describe how the drug exposure definition was developed. 7.1.b: Specify the data sources from which drug exposure information for individuals was obtained. 7.1.c: Describe the time window(s) during which an individual is considered exposed to the drug(s). The rationale for selecting a particular time window should be provided. The extent of potential left truncation or left censoring should be specified. 7.1.d: Justify how events are attributed to current, prior, ever, or cumulative drug exposure. 7.1.e: When examining drug dose and risk attribution, describe how current, historical or time on therapy are considered. 7.1.f: Use of any comparator groups should be outlined and justified. 7.1.g: Outline the approach	Pg 5

			used to handle individuals with more than one relevant drug exposure during the study period.	
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.	—	8.a: Describe the healthcare system and mechanisms for generating the drug exposure records. Specify the care setting in which the drug(s) of interest was prescribed.	Page 5 Appendix C and D
Bias				
9	Describe any efforts to address potential sources of bias.	—	—	Page 5
Study size				
10	Explain how the study size was arrived at.	—	—	Appendix E
Quantitative variables				
11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why.	—	—	Page 5/6
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) Cohort study—if applicable, explain how loss to follow-up was addressed. Case-control study—if applicable, explain how matching of cases and controls was addressed. Cross sectional study—if applicable, describe analytical methods	—	12.1.a: Describe the methods used to evaluate whether the assumptions have been met. 12.1.b: Describe and justify the use of multiple designs, design features, or analytical approaches.	Page 5/6

	taking account of sampling strategy. (e) Describe any sensitivity analyses.			
Data access and cleaning methods				
12	—	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.	—	Page 3/4
Linkage				
12	—	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.	—	Page 3/4
Results				
Participants				
13	(a) Report the numbers of individuals at each stage of the study (eg, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed). (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 individuals included in the study (that is, study population selection) including filtering based on data quality, data availability, and linkage. The selection of included individuals can be described in the text or by means of the study flow diagram.	—	Appendix E
Descriptive data				
14	(a) Give characteristics of study participants (eg, demographic, clinical, social) and information on exposures and potential confounders. (b) Indicate the number of participants with missing data for each variable of interest. (c) Cohort study—summarise follow-up time (eg, average and total amount).	—	—	Table 1 Page 6

Outcome data				
15	Cohort study—report numbers of outcome events or summary measures over time. Case-control study—report numbers in each exposure category, or summary measures of exposure. Cross sectional study—report numbers of outcome events or summary measures.	—	—	Table 2 Page 6/7
Main results				
16	(a) Give unadjusted estimates and, if applicable, confounder adjusted estimates and their precision (eg, 95% confidence intervals). Make clear which confounders were adjusted for and why they were included. (b) Report category boundaries when continuous variables are categorised. (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period.	—	—	Table 2 Table 3
Other analyses				
17	Report other analyses done—eg, analyses of subgroups and interactions, and sensitivity analyses.	—	—	Page 7
Discussion				
Key results				
18	Summarise key results with reference to study objectives.	—	—	Page 7
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.	19.1.a: Describe the degree to which the chosen database(s) adequately captures the drug exposure(s) of interest.	Page 8/9
Interpretation				

20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	—	20.a: Discuss the potential for confounding by indication, contraindication or disease severity or selection bias (healthy adherer/sick stopper) as alternative explanations for the study findings when relevant. **[A: Original text indicated this item was RECORD (ie, not RECORD-PE)?]**	Page 8/9
Generalisability				
21	Discuss the generalisability (external validity) of the study results.	—	—	Page 8
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.	—	—	Page 9/10
Accessibility of protocol, raw data, and programming code				
22	—	22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	—	Page 10

RECORD=reporting of studies conducted using observational routinely collected data; RECORD-PE=RECORD for pharmacoepidemiological research; STROBE=strengthening the reporting of observational studies in epidemiology.

Appendix C.B- Data Sources Used

Canadian Institute for Health Information Discharge Abstract Database/ Same Day Surgery	Diagnostic and procedural information for all hospitalizations and same day surgeries.
ICES-derived Physician Database	Physician related information such as birth date, sex, education, and specializations.
Canadian Institute for Health Information (Hospital Discharge Abstract Database and National Ambulatory Care Reporting System)	Information on emergency department visits.
Ontario Drug Benefit	Highly accurate records of all dispensed outpatient prescriptions covered through the Ontario Drug Benefit program, including denosumab and bisphosphonates. These are recorded with an error rate of <1%[47]
Ontario Health Insurance Plan	Diagnostic information and health claims for inpatient and outpatient physician services.
Ontario Registered Persons Database	Information on vital patient statistics including sex, birth and death dates for all residents who have been issued a health card
Ontario Marginalization Index	A geographically based index that quantifies degrees of marginalization (residential instability, material deprivation, dependency and ethnic concentration)
Ontario Laboratory Information Services	Database of inpatient and outpatient laboratory information (including creatinine, calcium, albumin, ionized calcium and parathyroid hormone).

Appendix C.C- Drug Identification Number (DIN) used to identify drugs of interest

Medication	**Drug Identification Numbers (DINs) Used**
Denosumab	02343541
Bisphosphonates	00582522, 01997629, 02176017, 02201011, 02201038, 02233055, 02239146, 02242518, 02245329, 02245330, 02246896, 02247323, 02247373, 02248625, 02248686, 02248728, 02248730, 02258102, 02258110, 02261715, 02263866, 02270129, 02273179, 02275279, 02276429, 02284006, 02286335, 02288087, 02288109, 02298376, 02298384, 02298392, 02299712, 02302209, 02314940, 02316838, 02319861, 02324199, 02327295, 02352966, 02353687, 02357984, 02368552, 02370417, 02377721, 02381486, 02381494, 02384701, 02384728, 02385031, 02388545, 02388553, 02394863, 02394871, 02397773, 02403633, 02403641, 02406306, 02413809, 02424177, 02428725, 02428733, 02429160, 02442760, 02454467, 0245447
Proton pump inhibitors	00000100, 00239616, 00846503, 02119579, 02165503, 02165511, 02190915, 02229453, 02230737, 02238525, 02239616, 02243796, 02243797, 02244522, 02245058, 02249472, 02260867, 02267233, 02280515, 02280523, 02285487, 02292920, 02293811, 02293838, 02295415, 02296446, 02296632, 02296640, 02298074, 02298082, 02299585, 02300486, 02300524, 02301083, 02305046, 02307871, 02308703, 02309866, 02310260, 02310805, 02310813, 02314177, 02314185, 02320614, 02320622, 02320851, 02329433, 02345579, 02345587, 02348691, 02353830, 02353849, 02356511, 02356538, 02357054, 02357682, 02357690, 02374870, 02381737, 02381745, 02385643, 02385651, 02395258, 02395266, 02402610, 02402629, 02403617, 02408392, 02408406, 02408570, 02412969, 02415208, 02416549, 02416565, 02417448, 02420198, 02422638, 02422646, 02428164, 02432404, 02433001, 02433028, 02437945, 02439549, 02440628, 02441853, 09857195, 09857267, 09857285, 09857314, 09857341, 09857342, 09857343, 09857464, 09857500, 09857530, 09857536, 09857776, 09857876, 09857777
Selective serotonin reuptake inhibitors	00636622, 01917021, 01919342, 01919369, 01940473, 01940481, 01962779, 01962817, 02018985, 02027887, 02087294, 02087375, 02087383, 02087391, 02103680, 02103702, 02132702, 02177579, 02177587, 02192764, 02216353, 02216361, 02216582, 02216590, 02218453, 02218461, 02223503, 02231192, 02231193, 02231328, 02231329, 02231330, 02237279, 02237280, 02237282, 02237398, 02237399, 02237400, 02237814, 02238280, 02238281, 02238282, 02239607, 02239608, 02239953, 02239954, 02240481, 02240484, 02240485, 02240682, 02240683, 02240849, 02240850, 02240907, 02240908, 02240909, 02241371, 02241374, 02242177, 02242178, 02242519, 02242520, 02242521, 02242823, 02242824, 02242825, 02243486, 02243487, 02244838, 02244839, 02244840, 02245102, 02245103, 02245111, 02245159, 02245160, 02245161, 02245203, 02245204, 02245205, 02245435, 02245436, 02245437, 02245787, 02245788, 02245789, 02245824, 02245825, 02245826, 02246056, 02246057, 02246594, 02246595, 02247054, 02247055, 02247751, 02247752, 02247811, 02247812, 02248010, 02248011, 02248012, 02248013, 02248014, 02248050, 02248051, 02248170, 02248171,

	02248451, 02248452, 02248557, 02248558, 02248944, 02251558, 02251566, 02252112, 02252120, 02254751, 02254778, 02255529, 02255537, 02262754, 02262762, 02263238, 02263254, 02269430, 02269449, 02273683, 02273691, 02273705, 02273969, 02273977, 02273985, 02275023, 02275031, 02275058, 02275562, 02275570, 02278545, 02278553, 02278561, 02282860, 02285622, 02285630, 02286076, 02287390, 02287404, 02287412, 02293218, 02293226, 02295016, 02295024, 02301830, 02301849, 02303817, 02303949, 02303965, 02304317, 02304325, 02304333, 02304686, 02304694, 02306239, 02306247, 02309467, 02309475, 02310279, 02310287, 02310295, 02310317, 02310325, 02310333, 02313405, 02313413, 02313561, 02313588, 02318180, 02318202, 02322781, 02322803, 02331683, 02331691, 02331705, 02331950, 02331977, 02353520, 02353539, 02353547, 02353660, 02353679, 02354713, 02354721, 02354748, 02355256, 02355264, 02355272, 02355280, 02357143, 02357151, 02357178, 02360020, 02360039, 02360047, 02364077, 02364085, 02368870, 02368889, 02371898, 02371901, 02374552, 02374560, 02374579, 02380072, 02380080, 02380099, 02380579, 02383241, 02383284, 02383292, 02385481, 02385503, 02385635, 02386402, 02390906, 02390914, 02390922, 02391449, 02391457, 02392917, 02397358, 02397374, 02399415, 02399423, 02399431, 02402378, 02402394, 02402408, 02405709, 02407418, 02407434, 02409011, 02409038, 02411954, 02411962, 02421380, 02421399, 02421747, 02423480, 02423502, 02427761, 02427788, 02427796, 02429705, 02429713, 02429780, 02429799, 02430118, 02430126, 02430541, 02430568, 02431785, 02431793, 02432420, 02434652, 02434660, 02438747, 02438755, 02440296, 02440318, 02452839, 02452847, 02452855, 02459361, 02459914, 02459922, 02469626, 02469634, 02469642, 09854126, 09854134, 09854142, 09854410, 09854428, 09854436, 09854539, 09857435, 09857443, 09857451, 09857460, 09857478, 09857486
Aromatase Inhibitors	00587729, 02128209, 02224135, 02231384, 02242705, 02309114, 02313049, 02320738, 02322315, 02328690, 02338459, 02338467, 02339080, 02343657, 02344815, 02347997, 02348969, 02351218, 02358514, 02361418, 02365650, 02372169, 02372282, 02373009, 02373424, 02374420, 02379104, 02379562, 02390183, 02393573, 02394898, 02404400, 02404990, 02407841, 02408473, 02417855, 02419726, 02421585, 02427818, 02428156, 02458799, 02459884
Anticonvulsants	00328162, 00602264, 00741701, 02142082, 02142104, 02142112, 02142120, 02230893, 02230894, 02230896, 02239907, 02239908, 02240115, 02243352, 02243353, 02245208, 02245209, 02245210, 02246897, 02246898, 02246899, 02246963, 02247027, 02247028, 02247029, 02248232, 02248233, 02248234, 02248860, 02248861, 02248862, 02256827, 02256835, 02256843, 02260050, 02260069, 02262991, 02263009, 02263017, 02263351, 02263378, 02263386, 02265494, 02265508, 02265516, 02267837, 02268418, 02268426, 02268434, 02268450, 02268485, 02271192, 02274183, 02274191, 02274205, 02279614, 02279630, 02279649, 02285924, 02285932, 02285940, 02287765, 02287773, 02287781, 02296101, 02296128, 02296136, 02315645, 02315653, 02315661, 02343010, 02343029, 02343037, 02345803, 02345838, 02345846, 02352850, 02352877,

	02352885, 02356856, 02356864, 02357615, 02357623, 02357631, 02357658, 02359596, 02359618, 02359626, 02359634, 02359642, 02360136, 02360144, 02360152, 02360179, 02360209, 02361159, 02361175, 02361183, 02361205, 02361248, 02369613, 02369621, 02369648, 02375249, 02375257, 02375265, 02381354, 02381362, 02381370, 02382210, 02382229, 02382237, 02382245, 02382253, 02390817, 02390825, 02390833, 02390841, 02390868, 02392801, 02392828, 02392836, 02392844, 02392860, 02394235, 02394243, 02394251, 02394278, 02394294, 02395738, 02395746, 02395754, 02396076, 02396084, 02396092, 02396106, 02396114, 02396122, 02398958, 02398966, 02398974, 02399776, 02399784, 02399792, 02402912, 02402920, 02402939, 02402955, 02402998, 02403005, 02403021, 02403048, 02404516, 02404524, 02404532, 02404540, 02404559, 02404567, 02405539, 02405547, 02405555, 02405563, 02405598, 02408651, 02408678, 02408686, 02408694, 02408708, 02414600, 02414619, 02414627, 02417529, 02417537, 02417545, 02417561, 02417618, 02423804, 02423812, 02424185, 02424207, 02426862, 02426870, 02426889, 02426897, 02431807, 02431815, 02431823, 02432099, 02432102, 02432110, 02433869, 02433877, 02433885, 02433907, 02435608, 02435616, 02435624, 02435977, 02435985, 02435993, 02436000, 02436019, 02440202, 02440210, 02440229, 02454653, 02454661, 02454688, 02461986, 02461994, 02462001, 09852409, 09854630, 09854661, 09900022, 09900044, 00002623, 00002631, 00010405, 00015261, 00015288, 00021032, 00022772, 00022780, 00022799, 00022802, 00022810, 00023442, 00023450, 00023485, 00023698, 00023795, 00023809, 00023817, 00027421, 00033707, 00093505, 00093521, 00093556, 00093564, 00178799, 00178802, 00178810, 00178829, 00245453, 00271276, 00271705, 00293903, 00320714, 00328162, 00344036, 00369810, 00396761, 00399310, 00402699, 00443832, 00443840, 00455881, 00497304, 00497495, 00504742, 00507989, 00588180, 00596418, 00596426, 00596434, 00602264, 00604542, 00604550, 00604577, 00604585, 00636576, 00645575, 00665088, 00741701, 00755583, 00773611, 00780626, 00782718, 00808520, 00849456, 02042355, 02042363, 02042568, 02052423, 02063735, 02063743, 02065819, 02068036, 02084260, 02084279, 02084287, 02088398, 02088401, 02100630, 02131048, 02131056, 02131064, 02136090, 02136104, 02139332, 02139391, 02140047, 02140055, 02140063, 02142082, 02142104, 02142112, 02142120, 02184648, 02194333, 02217414, 02229628, 02229936, 02229937, 02230033, 02230034, 02230768, 02230893, 02230894, 02230896, 02230988, 02231489, 02231540, 02231542, 02231543, 02231544, 02236507, 02236508, 02236807, 02236963, 02237830, 02237907, 02237908, 02238042, 02238048, 02238370, 02239517, 02239518, 02239519, 02239698, 02239699, 02239700, 02239701, 02239702, 02239703, 02239713, 02239714, 02239907, 02239908, 02240115, 02241882, 02241883, 02242067, 02242068, 02242069, 02242908, 02242909, 02243352, 02243353, 02243446, 02243447, 02243448, 02244138, 02244139, 02244140, 02244304, 02244305, 02244306, 02244403, 02244404, 02244513, 02244514, 02244515, 02244673, 02245208, 02245209, 02245210, 02246314, 02246315, 02246316, 02246897, 02246898, 02246899,

	02246963, 02247027, 02247028, 02247029, 02248232, 02248233, 02248234, 02248259, 02248260, 02248261, 02248457, 02248860, 02248861, 02248862, 02250896, 02255898, 02256142, 02256150, 02256169, 02256827, 02256835, 02256843, 02260050, 02260069, 02260883, 02260891, 02260905, 02261839, 02261847, 02261855, 02261863, 02262991, 02263009, 02263017, 02263351, 02263378, 02263386, 02265133, 02265141, 02265168, 02265494, 02265508, 02265516, 02267837, 02268418, 02268426, 02268434, 02268450, 02268485, 02271192, 02273853, 02274183, 02274191, 02274205, 02279614, 02279630, 02279649, 02284294, 02284308, 02284316, 02285819, 02285827, 02285835, 02285924, 02285932, 02285940, 02287021, 02287765, 02287773, 02287781, 02293358, 02296101, 02296128, 02296136, 02304090, 02315645, 02315653, 02315661, 02319055, 02319063, 02319071, 02321203, 02321211, 02321238, 02332582, 02332590, 02332604, 02343010, 02343029, 02343037, 02345803, 02345838, 02345846, 02352850, 02352877, 02352885, 02353245, 02353253, 02353261, 02356856, 02356864, 02357615, 02357623, 02357631, 02357658, 02359596, 02359618, 02359626, 02359634, 02359642, 02360136, 02360144, 02360152, 02360179, 02360209, 02361159, 02361175, 02361183, 02361205, 02361248, 02361469, 02361485, 02361493, 02367394, 02369613, 02369621, 02369648, 02375249, 02375257, 02375265, 02381354, 02381362, 02381370, 02382210, 02382229, 02382237, 02382245, 02382253, 02390817, 02390825, 02390833, 02390841, 02390868, 02391473, 02391481, 02391503, 02392801, 02392828, 02392836, 02392844, 02392860, 02394235, 02394243, 02394251, 02394278, 02394294, 02395738, 02395746, 02395754, 02396076, 02396084, 02396092, 02396106, 02396114, 02396122, 02398958, 02398966, 02398974, 02399776, 02399784, 02399792, 02402912, 02402920, 02402939, 02402955, 02402998, 02403005, 02403021, 02403048, 02404516, 02404524, 02404532, 02404540, 02404559, 02404567, 02405539, 02405547, 02405555, 02405563, 02405598, 02407515, 02408651, 02408678, 02408686, 02408694, 02408708, 02413620, 02413639, 02413647, 02414600, 02414619, 02414627, 02416840, 02416859, 02416867, 02417529, 02417537, 02417545, 02417561, 02417618, 02423804, 02423812, 02424185, 02424207, 02426862, 02426870, 02426889, 02426897, 02431408, 02431416, 02431424, 02431807, 02431815, 02431823, 02432099, 02432102, 02432110, 02433869, 02433877, 02433885, 02433907, 02435608, 02435616, 02435624, 02435977, 02435985, 02435993, 02436000, 02436019, 02440202, 02440210, 02440229, 02440717, 02440725, 02440733, 02454653, 02454661, 02454688, 02458926, 02458934, 02459019, 02460912, 02461986, 02461994, 02462001, 09852409, 09852549, 09853413, 09854630, 09854638, 09854661, 09857209, 09857210, 09857211, 09857235, 09857244, 09857245, 09857246, 09857247, 09857248, 09857250, 09857251, 09857252, 09857253, 09857254, 09857255, 09857256, 09857258, 09857259, 09857260, 09857261, 09857262, 09857263, 09857264, 09857296, 09900022, 09900044
Anticoagulants	00010308, 00010383, 00010391, 00585629, 00585637, 00585645, 00585653, 01918311, 01918338, 01918346, 01918354, 01918362, 02007959, 02240205, 02242680, 02242681, 02242682, 02242683,

	02242684, 02242685, 02242687, 02242924, 02242925, 02242926, 02242927, 02242928, 02242929, 02244462, 02244463, 02244464, 02244465, 02244466, 02244467, 02245618, 02265273, 02265281, 02265303, 02265311, 02265338, 02265346, 02287498, 02312441, 02316986, 02344025, 02344033, 02344041, 02344068, 02344076, 02344084, 02358808, 02377233, 02378604, 02378612, 02397714, 02377233, 02397714, 09857463
Activated Vitamin D	00481815, 00481823, 00824291, 00891738, 00891746, 02245686, 02399334, 02399342, 02431637, 02431645, 00474517, 00474525, 00759546, 02240329, 02242502, 02243790, , 00033057, 01928406, 02017601, 02243790,
Calcium Supplementation	00021253, 00027383, 00508640, 00541907, 00541915, 00640360, 00645923, 00645958, 02042983, 02042991
Loop Diuretics	00728276, 00728284, 02176076, 00016497, 02258528, 00012580, 00217743, 00289590, 00332275, 00337730, 00337749, 00344079, 00353612, 00362166, 00380016, 00380024, 00396249, 00396788, 00432342, 00527033, 01900943, 01987585, 01987615, 01987739, 01987798, 01988832, 02224690, 02224704, 02224720, 02224755, 09857208, 09857724, 09857725
Thiazide Diuretics	00010413, 00010421, 00293881, 00298964, 00337447, 00337455, 00360279, 00360287, 00398365, 00398373, 00016500, 00016519, 00021474, 00021482, 00092681, 00092703, 00263907, 00312800, 00326844, 00509353, 00584967, 02247386, 02247387, 00564966, 02049341, 02153483, 02179709, 02223597, 02223678, 02227339, 02231184, 02239619, 02239620, 02240067, 02245246, 02373904, 02373912, 00301663, 00301671, 00301698, 00888400, 00888419, 00888427
Levothyroxine	00009644, 00009652, 00009660, 00009687, 00009695, 00012289, 00012297, 00012300, 00012319, 00023949, 00023957, 00023965, 00027081, 00027103, 00212164, 00295582, 00631078, 00640425, 00640441, 00786578, 00786586, 01919458, 01919466, 01980890, 01980904, 01980912, 01980920, 01980939, 01980947, 01980955, 01980963, 01980971, 01980998, 01981005, 02171228, 02171236, 02172062, 02172070, 02172089, 02172097, 02172100, 02172119, 02172127, 02172135, 02172143, 02172151, 02213192, 02213206, 02213214, 02213222, 02213230, 02245948
Hyperthyroid therapy	00010200, 00010219, 00015741, 00518077, 02244323
Antihypertensives	00546283, 00546291, 00546305, 00670901, 00670928, 00695661, 00708879, 00708887, 00839329, 00839337, 00839388, 00839396, 00839418, 00839442, 00851639, 00851647, 00851655, 00851795, 00851833, 00884375, 00884413, 00885835, 00885843, 00885851, 00893595, 00893609, 00893617, 00893625, 01907107, 01907115, 01911465, 01911473, 01911481, 01913824, 01913832, 01913840, 01913859, 01942964, 01942972, 01942980, 01942999, 01947664, 01947672, 01947680, 01947699, 02019884, 02019892, 02019906, 02020025, 02045737, 02049333, 02049376, 02049384, 02050943, 02050951, 02050978, 02050986, 02103729, 02108194, 02123274, 02123282, 02163551, 02163578, 02163586, 02163594, 02181479, 02217481, 02217503, 02217511, 02221829, 02221837, 02221845,

	02221853, 02230203, 02230204, 02230205, 02230206, 02231459, 02231460, 02233005, 02233006, 02233007, 02237367, 02237368, 02237369, 02237861, 02237862, 02237863, 02239267, 02242733, 02242734, 02242788, 02242789, 02242790, 02242791, 02246568, 02246569, 02246624, 02247802, 02247803, 02247917, 02247918, 02247919, 02247945, 02247946, 02247947, 02248499, 02248500, 02248501, 02248502, 02251515, 02251531, 02251574, 02251582, 02255316, 02255324, 02255332, 02255944, 02255952, 02256797, 02256800, 02256819, 02261979, 02261987, 02262401, 02262428, 02266008, 02266016, 02266350, 02266369, 02266377, 02271443, 02271451, 02271478, 02273918, 02274833, 02274841, 02274868, 02275252, 02275260, 02280442, 02280450, 02280469, 02283131, 02283158, 02283166, 02283174, 02283182, 02283778, 02283786, 02283794, 02283891, 02284987, 02285061, 02285088, 02285096, 02285118, 02285126, 02285134, 02285215, 02285223, 02287692, 02287706, 02287714, 02287722, 02287927, 02287935, 02287943, 02289199, 02289202, 02289229, 02289261, 02289288, 02289296, 02290332, 02290340, 02290987, 02290995, 02291002, 02291010, 02291134, 02291142, 02291150, 02291398, 02291401, 02291428, 02291436, 02291878, 02291886, 02291894, 02291908, 02292203, 02292211, 02292238, 02294230, 02294249, 02294257, 02294524, 02294532, 02294591, 02295369, 02295482, 02295490, 02295504, 02295512, 02297736, 02297744, 02299372, 02299879, 02299887, 02299895, 02299933, 02299941, 02299968, 02299976, 02299984, 02299992, 02300001, 02300028, 02300036, 02300044, 02300052, 02300060, 02300079, 02300087, 02300095, 02300109, 02300117, 02300125, 02300133, 02300141, 02300680, 02301148, 02301156, 02301164, 02301172, 02301768, 02301776, 02302136, 02302144, 02302365, 02302373, 02310503, 02310511, 02310538, 02310546, 02313731, 02321653, 02325748, 02325756, 02325764, 02331004, 02331012, 02331101, 02331128, 02331136, 02331144, 02332167, 02332175, 02332183, 02332299, 02332302, 02332310, 02332329, 02332566, 02332574, 02342138, 02342146, 02342154, 02342162, 02342170, 02352230, 02352249, 02352257, 02352265, 02357763, 02357771, 02357798, 02361531, 02361558, 02361566, 02374846, 02374854, 02374862, 02387387, 02387395, 02387409, 02387417, 02388332, 02388340, 02388359, 02388367, 02388375, 02394472, 02394480, 02394499, 02408767, 02408783, 02420457, 02420465, 02420473, 02420481, 02421305, 02421313, 02421321, 02438860, 02438879, 02438887, 02438895, 02449439, 02449463, 02459817, 02459825, 02459833, 02464020, 02464039, 02464985, 02464993, 02465000, 02469081, 02470225, 02470233, 02470241, 02470411, 02470438, 02470446, 02470675, 02470683, 02470691, 09853685, 09853960, 09854010, 09857272, 09857286, 09857287, 02182815, 02182874, 02182882, 02230047, 02236808, 02236809, 02237923, 02237924, 02237925, 02239090, 02239091, 02239092, 02240431, 02240432, 02240769, 02240770, 02241007, 02241818, 02241819, 02241900, 02241901, 02243942, 02244021, 02244344, 02244781, 02244782, 02246955, 02253631, 02280213, 02289504, 02297841, 02308908, 02308916, 02309750, 02309769, 02309777, 02311658, 02313006, 02313014, 02313332, 02313340, 02313359, 02313375,

	02313383, 02315971, 02315998, 02316005, 02316013, 02316021, 02316048, 02316390, 02316404, 02316412, 02317060, 02317079, 02317087, 02318660, 02318679, 02318709, 02319616, 02319624, 02319632, 02320177, 02320185, 02326957, 02326965, 02326973, 02327902, 02328070, 02328089, 02328100, 02328461, 02328488, 02328496, 02328518, 02328526, 02328534, 02330288, 02330512, 02330520, 02330539, 02332922, 02332957, 02337428, 02337436, 02337444, 02337495, 02337509, 02337517, 02344564, 02347296, 02347318, 02347326, 02353504, 02353512, 02354829, 02354837, 02354845, 02356651, 02356678, 02356686, 02356694, 02356708, 02356716, 02356724, 02356732, 02356759, 02356767, 02356775, 02356996, 02357003, 02357011, 02357038, 02357046, 02357399, 02357402, 02357410, 02357968, 02357976, 02358263, 02362449, 02363100, 02363119, 02363208, 02363216, 02363224, 02365340, 02365359, 02365367, 02366312, 02366320, 02366339, 02367866, 02368277, 02368285, 02368293, 02371022, 02371030, 02371049, 02371057, 02371235, 02371243, 02371251, 02371529, 02371537, 02371545, 02373564, 02373572, 02373734, 02373742, 02373750, 02373769, 02373777, 02374897, 02375958, 02375966, 02376520, 02376539, 02376547, 02376555, 02376717, 02376725, 02377144, 02377152, 02378078, 02378086, 02378094, 02379058, 02379120, 02379139, 02379147, 02379155, 02379252, 02379260, 02379279, 02379287, 02379295, 02380684, 02380692, 02380706, 02380714, 02380838, 02382547, 02382555, 02382563, 02382571, 02382598, 02383535, 02383543, 02383551, 02386496, 02386518, 02386526, 02386534, 02386968, 02386976, 02386984, 02387646, 02387654, 02387662, 02388251, 02388278, 02388286, 02388650, 02389657, 02389665, 02389673, 02391171, 02391198, 02391201, 02391228, 02391236, 02391244, 02391295, 02392224, 02392232, 02392240, 02392267, 02392992, 02393018, 02393026, 02393247, 02393255, 02393263, 02393271, 02393557, 02393565, 02395126, 02395134, 02395541, 02395568, 02395576, 02398834, 02398842, 02398850, 02399105, 02401665, 02401673, 02403323, 02403331, 02403358, 02404451, 02404478, 02404486, 02405733, 02405741, 02405768, 02406098, 02406101, 02406128, 02406810, 02406829, 02406837, 02407485, 02407493, 02408112, 02408120, 02408139, 02408147, 02408155, 02408244, 02408252, 02408775, 02414228, 02414236, 02414244, 02417340, 02418193, 02418207, 02418215, 02418223, 02418231, 02418258, 02419114, 02419122, 02420023, 02420031, 02420082, 02420090, 02420732, 02420740, 02421038, 02421046, 02421054, 02422468, 02422484, 02422980, 02422999, 02423006, 02423642, 02423650, 02423669, 02424967, 02424975, 02424983, 02426595, 02426609, 02426617, 02427087, 02427095, 02427109, 02432897, 02432900, 02433214, 02433222, 02434164, 02434172, 02442191, 02442205, 02443112, 02443120, 02443139, 02443414, 02443422, 02443864, 02443872, 02445786, 02445794, 02445980, 02447878, 02447886, 02447894, 02453452, 02453460, 02453568, 02453576, 02453606, 02453614, 02453622, 02456389, 02456397, 02461307, 02461315, 02461641, 02461668, 00002658, 00002666, 00313602, 00353914, 00353922, 00397423, 00397431, 00402540, 00402567, 00402575, 00402583, 00402605, 00402753, 00402761,

	00402788, 00417270, 00417289, 00443174, 00451193, 00451207, 00456578, 00463256, 00465313, 00465321, 00483923, 00486833, 00489859, 00495611, 00496480, 00496499, 00496502, 00497827, 00504335, 00511668, 00520683, 00523372, 00523380, 00523399, 00523402, 00534560, 00534579, 00534587, 00549657, 00566950, 00568627, 00568635, 00582255, 00582263, 00582271, 00587931, 00603643, 00603651, 00607126, 00618632, 00618640, 00637661, 00638625, 00638633, 00648035, 00648043, 00658855, 00663719, 00695645, 00695653, 00695688, 00726559, 00726567, 00740675, 00749354, 00751170, 00751286, 00755826, 00755834, 00755842, 00755850, 00755869, 00755877, 00755885, 00755893, 00771333, 00771341, 00773689, 00773697, 00782467, 00782475, 00782505, 00818593, 00818607, 00818615, 00842648, 00842656, 00851663, 00851671, 00851698, 00865605, 00865613, 00869007, 00869015, 00869023, 00886009, 00886114, 00886122, 00886130, 00886149, 00893773, 00893781, 00897272, 01908448, 01910140, 01910159, 01910167, 01912054, 01912062, 01924915, 01924923, 01924931, 01926543, 01926551, 01926578, 01947796, 01947818, 01947826, 02031159, 02031167, 02036290, 02036436, 02036444, 02039532, 02039540, 02042177, 02042193, 02042207, 02042215, 02042231, 02042258, 02042266, 02042274, 02042282, 02042290, 02044609, 02044617, 02044625, 02048515, 02048523, 02049961, 02049988, 02057808, 02057816, 02057824, 02083345, 02083353, 02084228, 02084236, 02091518, 02106272, 02106280, 02123290, 02123304, 02126753, 02126761, 02145413, 02145421, 02146894, 02147432, 02147602, 02147610, 02147629, 02163772, 02165546, 02165554, 02165562, 02166712, 02166720, 02167794, 02170841, 02171791, 02171805, 02171880, 02171899, 02174545, 02174553, 02204517, 02204525, 02204533, 02210428, 02220679, 02220687, 02229650, 02229651, 02229652, 02229653, 02229778, 02229779, 02229780, 02230076, 02230077, 02230448, 02230449, 02230650, 02230803, 02230804, 02231181, 02231182, 02231536, 02231537, 02231539, 02231714, 02231715, 02231731, 02231733, 02234013, 02237600, 02237601, 02237721, 02237722, 02237723, 02237885, 02237886, 02237887, 02237991, 02238316, 02238318, 02238326, 02238327, 02238415, 02240249, 02240808, 02240809, 02240810, 02240811, 02241148, 02241149, 02241574, 02241575, 02241715, 02241716, 02242275, 02242276, 02243538, 02243539, 02245914, 02245915, 02245916, 02245917, 02246010, 02246529, 02246530, 02246531, 02246532, 02247439, 02247440, 02247875, 02247876, 02247933, 02247934, 02247935, 02247936, 02248347, 02248752, 02248753, 02248755, 02248763, 02248764, 02252309, 02252317, 02252325, 02252333, 02253518, 02253526, 02255545, 02255553, 02256134, 02256177, 02257599, 02257602, 02257610, 02257858, 02261782, 02261790, 02261804, 02267470, 02267489, 02267985, 02267993, 02268027, 02268035, 02268043, 02268051, 02270625, 02270633, 02278251, 02285169, 02285177, 02286246, 02286254, 02286262, 02290812, 02302632, 02302640, 02302918, 02302926, 02303396, 02303418, 02331624, 02347512, 02347520, 02347555, 02347571, 02350394, 02350408, 02354187, 02354195, 02356821, 02356848, 02364913, 02364921, 02364948, 02364956, 02367564, 02367572,

	02368021, 02368048, 02368625, 02368641, 02368668, 02368897, 02368900, 02368919, 02368927, 02371987, 02371995, 02384418, 02384426, 02418495, 02418509, 02418517, 02418525, 02466465, 02466473, 09851453, 09857298, 09857333, 09857512, 09857513, 00299790, 00554316, 00554324, 00557633, 00587753, 00587761, 00596442, 00613258, 00692727, 00692735, 00725110, 00728314, 00728322, 00728330, 00742554, 00755907, 00756830, 00771376, 00771384, 00782483, 00782491, 00812331, 00812358, 00851779, 00851787, 00852082, 00862924, 00862932, 00864013, 00864021, 00865591, 00867365, 00867373, 00878928, 00878936, 00886033, 00886041, 00886068, 00886076, 00888524, 00888532, 01910221, 01911813, 01913131, 01913158, 01917064, 01917072, 01934317, 01946307, 01989596, 01989618, 02009315, 02009323, 02047462, 02048620, 02057778, 02057786, 02069539, 02097214, 02097222, 02097249, 02097257, 02097265, 02097273, 02097370, 02097389, 02100487, 02100495, 02146916, 02146924, 02154390, 02154404, 02155869, 02155877, 02155885, 02155893, 02155907, 02155923, 02155990, 02156059, 02156067, 02181525, 02197448, 02210347, 02210355, 02210363, 02211920, 02221985, 02221993, 02222000, 02222957, 02222965, 02222973, 02229406, 02229407, 02229408, 02229526, 02229781, 02229782, 02229783, 02229784, 02229997, 02230031, 02230032, 02230997, 02230998, 02230999, 02231052, 02231053, 02231054, 02231150, 02231151, 02231152, 02231154, 02231155, 02231676, 02231677, 02231743, 02231744, 02231745, 02235897, 02235898, 02237618, 02237791, 02237921, 02237922, 02242538, 02242539, 02242540, 02242541, 02243338, 02243339, 02243340, 02243341, 02245918, 02245919, 02245920, 02245921, 02245922, 02246894, 02246895, 02250497, 02250500, 02254808, 02254816, 02254824, 02254832, 02256738, 02256746, 02256754, 02256762, 02256770, 02259605, 02259613, 02271605, 02271613, 02271621, 02271648, 02271656, 02272113, 02272121, 02273233, 02273241, 02273268, 02273276, 02273284, 02273292, 02273306, 02273314, 02273373, 02273381, 02280132, 02280140, 02280264, 02280272, 02284065, 02284073, 02284383, 02284391, 02291037, 02291045, 02291053, 02291061, 02291088, 02297485, 02297493, 02321149, 02321858, 02321866, 02325926, 02326779, 02326787, 02331071, 02331098, 02331284, 02331292, 02331934, 02331942, 02342790, 02342804, 02349167, 02355752, 02355760, 02355779, 02355787, 02357194, 02357208, 02357712, 02357720, 02362651, 02362678, 02362759, 02362767, 02362775, 02362783, 02362791, 02362805, 02362813, 02362821, 02370441, 02370492, 02370506, 02370514, 02370522, 02370611, 02370638, 02370646, 02370654, 02371715, 02371723, 02378760, 02378779, 02397072, 02397080, 02404222, 02404230, 02404249, 02404257, 02411253, 02411261, 02411288, 02411296, 02411318, 02411326, 02411334, 02411342, 02426986, 02426994, 02429217, 02429225, 02450488, 02450496, 02452367, 02452375, 02452383, 02460289, 02465353, 02465361, 02465388, 02465396, 02465418, 02469049, 09857203, 09857204
Anti-Androgens	00637726, 00704423, 00704431, 00863890, 00863904, 01989642, 01989650, 02184478, 02221861, 02221888, 02229449, 02229723, 02230089, 02230104, 02232872, 02238560, 02245898, 02270226,

	02274337, 02275589, 02276089, 02277700, 02296063, 02302403, 02325985, 02357216, 02371324, 02428709
Antiplatelet Agents	00067385, 00067393, 00452092, 00452106, 00571237, 00571245, 00579327, 00601845, 00784435, 00895644, 00895652, 00895660, 02238682, 02242119, 02252767, 02293161, 02303027, 02348004, 02351536, 02359316, 02379813, 02408910, 02412942, 02415550, 02416387, 02422255, 09852565, 00911759, 01911759, 02162776, 02194422, 02236848, 02237560, 02237701, 02239744, 02243327, 02243587, 02236859, 02236860, 02260107, 02349124, 02368544
Benzodiazepines	00012629, 00012637, 00012645, 00012696, 00012718, 00012874, 00013277, 00013285, 00013293, 00013463, 00013471, 00013498, 00013757, 00013765, 00013773, 00020915, 00020923, 00020931, 00115630, 00231363, 00264911, 00264938, 00264946, 00272434, 00272442, 00272450, 00272639, 00272647, 00280429, 00295051, 00295698, 00295701, 00348325, 00348333, 00362158, 00382825, 00382841, 00396230, 00398403, 00398411, 00398438, 00399124, 00399728, 00402680, 00402737, 00402745, 00405329, 00405337, 00443158, 00466891, 00466905, 00483818, 00483826, 00483893, 00483907, 00483915, 00496529, 00496537, 00496545, 00496553, 00500852, 00511528, 00511536, 00512559, 00514519, 00514527, 00518123, 00518131, 00521698, 00521701, 00522724, 00522988, 00522996, 00548359, 00548367, 00557757, 00557765, 00557773, 00602825, 00604453, 00604461, 00614351, 00614378, 00628190, 00628204, 00628212, 00637742, 00637750, 00655740, 00655759, 00655767, 00677477, 00677485, 00682314, 00711101, 00722138, 00728187, 00728195, 00728209, 00766011, 00784516, 00808563, 00808571, 00813958, 00846392, 00860689, 00860697, 00860700, 00865397, 00865400, 00865672, 00865680, 00865699, 00872431, 00886084, 00886092, 00891797, 00893706, 01913239, 01913247, 01913484, 01913492, 01913506, 01926799, 01989634, 01995227, 02008203, 02041405, 02041413, 02041421, 02041448, 02041456, 02041464, 02041472, 02043653, 02043661, 02043688, 02048701, 02048736, 02065614, 02103656, 02103737, 02137534, 02137542, 02145227, 02145243, 02167808, 02167816, 02167824, 02171856, 02171864, 02171872, 02173344, 02173352, 02177153, 02177161, 02177188, 02177889, 02177897, 02192705, 02192713, 02192721, 02207818, 02216167, 02218313, 02221799, 02223570, 02223589, 02225964, 02225972, 02229455, 02229456, 02229654, 02229655, 02230024, 02230025, 02230074, 02230075, 02230095, 02230102, 02230366, 02230369, 02230584, 02230585, 02230950, 02230951, 02231615, 02231616, 02233960, 02233985, 02234003, 02234007, 02236948, 02238162, 02238334, 02238596, 02238797, 02239024, 02239025, 02240285, 02240286, 02240606, 02242481, 02242905, 02243023, 02243024, 02243254, 02243278, 02243426, 02244474, 02244638, 02244814, 02244815, 02245077, 02245230, 02245231, 02246534, 02251450, 02251469, 02257572, 02257580, 02267918, 02267926, 02270641, 02270676, 02271931, 02271958, 02273039, 02273047, 02282445, 02296616, 02303337, 02344122, 02345676, 02349205, 02356805, 02386143, 02386771, 02386798, 02386917, 02391716, 02391724, 02400111, 02400138, 02406969, 02406977, 02410753, 02410761, 02417634, 02417642, 09852395, 09853340,

	09853430, 09857216, 09857225, 09857240, 09857436, 09857437, 09857438
Cholinesterase Inhibitors	02232043, 02232044, 02242115, 02242116, 02242117, 02242118, 02244298, 02244299, 02244300, 02245240, 02266717, 02266725, 02266733, 02305984, 02305992, 02306018, 02306026, 02306034, 02306042, 02306050, 02306069, 02311283, 02311291, 02311305, 02311313, 02316943, 02316951, 02316978, 02322331, 02322358, 02324563, 02324571, 02324598, 02324601, 02328666, 02328682, 02332809, 02332817, 02332825, 02332833, 02336715, 02336723, 02336731, 02336758, 02339439, 02339447, 02339455, 02340607, 02340615, 02359472, 02359480, 02362260, 02362279, 02377950, 02377969, 02377977, 02381508, 02381516, 02397595, 02397609, 02398370, 02398389, 02398397, 02400561, 02400588, 02401614, 02401622, 02401630, 02401649, 02402092, 02402106, 02402645, 02402653, 02404419, 02404427, 02406985, 02406993, 02407000, 02407019, 02412853, 02412861, 02416948, 02416956, 02420821, 02420848, 02420856, 02425157, 02425165, 02425173, 02426846, 02426854, 02426943, 02426951, 02428482, 02428490, 02439557, 02439565
Antiarrhythmics	00004782, 00021733, 00023868, 00026131, 00026883, 00029076, 00029181, 00094412, 00249580, 00296031, 00311731, 00346837, 00353523, 00382876, 00396370, 00396389, 00439363, 00441740, 00584231, 00598941, 00598968, 00599956, 00599964, 00603708, 00603716, 00619760, 00628220, 00638676, 00638684, 00638692, 00639885, 00704644, 00705934, 00713325, 00713333, 00713341, 00817147, 01913883, 01966197, 01966200, 01989545, 01989553, 01989561, 02030799, 02030802, 02030810, 02036282, 02224801, 02224828, 02224836, 02230359, 02230360, 02231690, 02231692, 02239835, 02240071, 02240604, 02242472, 02243324, 02243325, 02243727, 02243728, 02243836, 02245372, 02245373, 02245781, 02246194, 02275538, 02275546, 02294559, 02294575, 02343053, 02343061, 02364336, 02457164, 02457172, 02459957, 02459965
Anticholinergics	00004405, 00004758, 00014656, 00015040, 00015059, 00016128, 00016357, 00021911, 00021938, 00025550, 00124982, 00271314, 00280445, 00306290, 00426857, 00428086, 00485012, 00545058, 00545074, 00576158, 00587354, 00649392, 00706531, 00731439, 00885398, 01927744, 01950681, 02026759, 02097141, 02097168, 02097176, 02126222, 02210479, 02216221, 02231135, 02231136, 02231245, 02231494, 02238903, 02239131, 02239627, 02243827, 02246793, 02247686, 02435381
Testosterone	00005622, 00005630, 00029246, 00030783, 00030902, 00782327, 00985007, 01977571, 02239653, 02245345, 02245346, 02245972, 02280248, 02322498, 02463792, 02463806, 09850325, 09850511, 09852271, 09852514, 09853006
Insulin	00446564, 00446572, 00446580, 00446599, 00446602, 00446610, 00513644, 00514535, 00514551, 00542911, 00552259, 00552267, 00552275, 00586714, 00587737, 00612189, 00612197, 00612200, 00612219, 00612227, 00612235, 00612243, 00612251, 00612278, 00614416, 00632651, 00632678, 00632686, 00632694, 00644358, 00646148, 00648094, 00650935, 00733075, 00773654, 00795879,

	00889091, 00889105, 00889113, 00889121, 00980765, 00981044, 00981052, 00983780, 00983810, 00983870, 01934066, 01934074, 01934082, 01934090, 01934104, 01934112, 01959212, 01959220, 01959239, 01962639, 01962647, 01962655, 01962663, 01985930, 01985949, 01985957, 01985965, 01985973, 01985981, 01986805, 01986813, 01986821, 02024217, 02024225, 02024233, 02024241, 02024268, 02024276, 02024284, 02024292, 02024306, 02024314, 02024322, 02025248, 02229704, 02229705, 02240294, 02240297, 02244353, 02245397, 02245689, 02251930, 02265435, 02271842, 02275864, 02275872, 02279460, 02279479, 02294338, 02294346, 02377209, 02403412, 02403420, 02403439, 02412829, 02439611, 02441829, 02444844, 02444852, 02467879, 02467887, 09851925, 09852557, 09853715, 09853766, 09853774, 09853782, 09853804, 09853812, 09853839, 09853847, 09853855, 09853863, 09853871, 09857352, 09857353, 09857355, 09900003, 09857748, 09857749
Thiazolidinediones	02241112, 02241113, 02241114, 02242572, 02242573, 02242574, 02274914, 02274922, 02274930, 02297906, 02297914, 02297922, 02298279, 02298287, 02298295, 02301423, 02301431, 02301458, 02302861, 02302888, 02302896, 02302942, 02302950, 02302977, 02303124, 02303132, 02303140, 02303442, 02303450, 02303469, 02307677, 02307723, 02326477, 02326485, 02326493, 02339587, 02339595, 02365529, 02365537, 02375850, 02375869, 02375877, 02384906, 02384914, 02384922, 02391600, 02397307, 02403366, 02403374, 02403382, 02434156
Sodium Glucose Cotransporter-2	02425483, 02425491, 02435462, 02435470, 02443937, 02443945, 02449935, 02449943, 02456575, 02456583, 02456591, 02456605, 02456613, 02456621,
Repaglinide	02239924, 02239925, 02239926, 02321475, 02321483, 02321491, 02354926, 02354934, 02354942, 02355663, 02355671, 02355698, 02357453, 02357461, 02357488, 02424258, 02424266, 02424274
Sulfonylureas	02245272, 00012599, 00454753, 00720933, 00720941, 00808733, 00808741, 01900927, 01900935, 01913654, 01913662, 01913670, 01913689, 01987534, 01987836, 02020734, 02020742, 02224550, 02224569, 02230036, 02230037, 02236733, 02236734, 02248008, 02248009, 02350459, 02350467, 00021350, 00024708, 00024716, 00312711, 00377937, 00399302, 00012602, 00013889, 00021849, 00093033, 00312762, 00765996, 02229519, 02238103, 02242987, 02245247, 02287072, 02294400, 02297795, 02356422, 02407124, 02423286, 02423294, 02429764, 02439328, 02461323, 02461331
Inhaled corticosteroids	01950002, 01978918, 01978926, 02174758, 02174766, 02174774, 02213591, 02213605, 02213613, 02213710, 02213729, 02215039, 02215047, 02215055, 02216531, 02229099, 02237245, 02237246, 02237247, 02242029, 02242030, 02244291, 02244292, 02244293, 02285606, 02285614, 02303671, 02417316, 02465957, 09857675, 09857676, 09857677, 09857679, 09857680, 02465949,
Aromatase Inhibitors	00587729, 02128209, 02224135, 02231384, 02242705, 02309114, 02313049, 02320738, 02322315, 02328690, 02338459, 02338467, 02339080, 02343657, 02344815, 02347997, 02348969, 02351218, 02358514, 02361418, 02365650, 02372169, 02372282, 02373009, 02373424, 02374420, 02379104, 02379562, 02390183, 02393573,

	02394898, 02404400, 02404990, 02407841, 02408473, 02417855, 02419726, 02421585, 02427818, 02428156, 02458799, 02459884
Oral Corticosteroids	00015016, 00015024, 00016438, 00016446, 00016462, 00021695, 00028185, 00029351, 00030910, 00030929, 00030988, 00036129, 00036366, 00093629, 00210188, 00212385, 00232378, 00249963, 00252417, 00271373, 00280437, 00285471, 00295094, 00312770, 00349100, 00354309, 00489158, 00501050, 00504416, 00550957, 00598194, 00610623, 01964070, 01964976, 02086026, 02152541, 02194082, 02194090, 02229293, 02230619, 02240684, 02240687, 02245532, 02250055, 02261081, 09854537, 09857797, 09857798, 09857799
Estrogen Replacement	00002089, 00002569, 00002577, 00002585, 00002593, 00017965, 00017973, 00022608, 00022632, 00024007, 00028215, 00028223, 00028231, 00028630, 00028681, 00029238, 00030333, 00034207, 00108278, 00134198, 00265470, 00265489, 00282677, 00282685, 00297143, 00315966, 00317047, 00340731, 00340758, 00340766, 00340847, 00343536, 00343838, 00353027, 00372838, 00372846, 00373265, 00373273, 00403466, 00441295, 00464791, 00464805, 00469327, 00471526, 00531006, 00531014, 00538582, 00538590, 00602957, 00602965, 00620947, 00695734, 00707503, 00707600, 00716758, 00756792, 00756849, 00756857, 00782416, 00782424, 00782432, 00782440, 00990531, 01968440, 01992872, 02016958, 02028700, 02029421, 02042320, 02042339, 02042479, 02042487, 02042533, 02042541, 02043033, 02043041, 02043394, 02043408, 02043424, 02043440, 02043726, 02043734, 02061031, 02089769, 02089777, 02089793, 02108186, 02148587, 02148595, 02168898, 02187086, 02187094, 02187108, 02187116, 02188724, 02188732, 02189054, 02189062, 02204401, 02204428, 02204436, 02204444, 02225190, 02231509, 02231510, 02233542, 02236974, 02236975, 02237807, 02237808, 02238704, 02241332, 02241835, 02241837, 02242531, 02242878, 02242879, 02243529, 02243530, 02243722, 02243724, 02243999, 02244000, 02244001, 02244002, 02245676, 02246967, 02246968, 02246969, 02247499, 02257238, 02258560, 02258587, 02261723, 02261731, 02272903, 02290308, 02295946, 02295954, 02298538, 02298546, 02317192, 02317206, 02321157, 02325462, 02385058, 02385066, 02387085, 02387093, 02388138, 02388146, 02391767, 02396491, 02396610, 02401967, 02401975, 02410249, 02410257, 02414678, 02414686, 02414694, 02415380, 02449048, 02449056, 02449064, 02387875, 02387883, 02401185, 02401207
Metformin and metformin combinations	00314552, 00990329, 02045710, 02099233, 02148765, 02162822, 02162849, 02167786, 02223562, 02229516, 02230026, 02230475, 02233999, 02242794, 02242974, 02246820, 02257726, 02269031, 02333856, 02333864, 02333872, 02353377, 02378620, 02378841, 02379767, 02380196, 02380722, 02388766, 02389169, 02389177, 02389185, 02403250, 02403269, 02403277, 02416786, 02416794, 02416808, 02421828, 02438275, 02449935, 02449943, 02456575, 02456583, 02456591, 02456605, 02456613, 02456621, 02449935, 02449943, 02456575, 02456583, 02456591, 02456605, 02456613, 02456621

Selective Estrogen Receptor Modulators	02239028, 02279215, 02312298, 02358840, 02358921
Intravenous bisphosphonates	01974491, 02059762, 02059770, 02059789, 02242725, 02244550, 02244551, 02244552, 02248296, 02249677, 02249685, 02264951, 02264978, 02264986, 02269198, 02401606, 02407639, 02408082, 02413701, 02415100, 02415186, 02421550, 02422425, 02422433, 09854639, 09857301, 09857304, 09857305, 09857399, 09857402, 09857403

Appendix C.D- Codes used to identify baseline characteristics

Diagnosis	**ICD-10 Codes**	**CCI**	**OHIP Feecodes**	**OHIP Diagnosis Codes**	**OLIS Observation Code**
Arrythmia	I48, I44, I45, I47, I4900, I4901, I491, I492, I493, I494, I498, I499, R000, R001		G178, G179, G249, G261, G259, Z443, Z431, Z437		
Chronic Liver Disease	B16, B17, B18, B19, I85, R17, R18, R160, R162, B942, Z225, E831, E830, K70, K713, K714, K715, K717, K721, K729, K73, K74, K753, K754, K758, K759, K76, K77		Z551, Z554	571, 573, 070	
COPD	J41, J43, J44				
Acute Kidney Injury	N17				
Epilepsy	G40			345	

Paget's Disease	M88			731	
Coronary Artery Disease	I21, I22, Z955, T822	1IJ50, 1IJ76	R741, R742, R743, G298, E646, E651, E652, E654, E655, Z434, Z448	410, 412	
Rheumatoid Arthritis	M05, M06			714	
Malabsorption Syndrome	K90			579	
Anxiety and Depression	F063, F064, F204, F313, F314, F315, F32, F33, F341, F400, F401, F402, F408, F409, F410, F411, F412, F413, F418, F419, F420, F421, F422, F428, F429, F430, F431, F432			311	
Hypotension	I95				
Parkinson's Disease	G20, F023			332	
Thyrotoxicosis	E05, E062			242	
Hypothyroidism	E00, E01, E02, E03, E890				
Hyperparathyroidism	E210, E211, E212, E213				
Hypoparathyroidism	E20				
Disorders of calcium metabolism	ICD10: E58, E835				
Multiple Sclerosis	G35			340	
Vitamin D Deficiency	E55				
Osteoporosis	M80, M81, M82			733	

Stroke/TIA	I60, I600, I601, I602, I603, I604, I605, I606, I607, I608, I609, I61, I610, I611, I612, I613, I614, I615, I616, I618, I619, I630, I631, I632, I633, I634, I635, I638, I639, I64, H341, G450, G451,G452, G453, G458, G459, H340			436, 432, 435	
Syncope	R55				
Alcohol Misuse	E244, E512, E52, F10, G312, G621, G721, I426, K292, K70, K860, T51, X45, X65, Y15, Y573, Z502, Z714, Z721				
Systemic Lupus Erythematosus	M32				
Fall	W00, W01, W02, W03, W04, W05, W06, W07, W08, W09, W10, W11, W12, W13, W14, W15, W16, W17, W18, W19				

Hip Fracture	S720, S721, S722				
Spine Fracture	S220, S221, S320, S327, S328			805	
Upper Arm/ Shoulder Fracture	S422			812	
Wrist and Forearm fracture	S52			813	
Pelvic Fracture	S321, S323, S324, S325, S327, S328			808	
Chronic Dialysis	Z49, Z992	1PZ21	R849, G323, G325, G326, G860, G862, G865 G863, G866, G330, G331, G333, G861, G082, G083, G085, G090, G091, G092, G093, G094, G095, G096, G294, G295, G864, H540, H740		
Nephrologist Visit			A160, A161, A163, A164, A165, A166,		

			A168, A865, C160, C161, C162, C163, C164, C165, C166, C167, C169, C865, W165, W160, W865, W166, W862, W864, W867, W869 , W164, W162, W161, W163, W168 A130, A131, A133, A134, A135, A136, A138, A435, C121, C122, C123, C124, C130, C131, C132, C133, C134, C135, C136, C137, C138,		

			C139, C142, C143, C168, C435, C982, W121, W130, W131, W132, W133, W134, W138, W232, W234, W235, W236, W237, W239, W435, W972, W982		
Lab testing					
Calcium	L045, L046				29265-6, 1995-0, 19072-8, 1994-3, 47598-8, 34581-9, 59473-9, 41645-3, 12180-6, 13959-2, 47596-2, 53140-0, 41644-6, 53139-2, 2000-8
Creatinine	L065, L067, L068				14682-9
Carotid Ultrasound		3JE30, 3JG30	J201, J501, J190, J191, J490,		

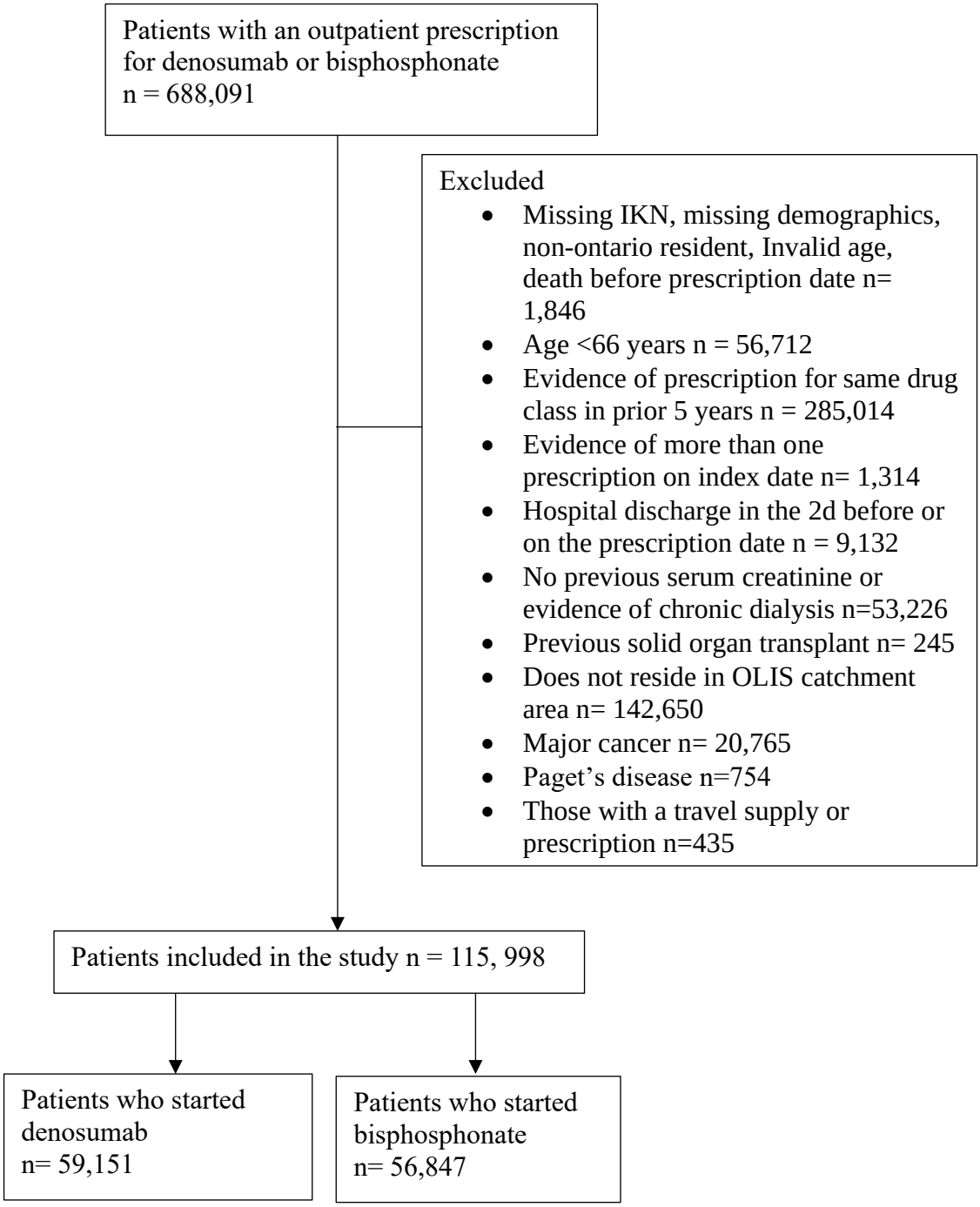
			J491, J492		
CT scans			X126, X409, X410, X188, X400, X401, X402, X405, X408, X124, X403, X404, X231, X232, X233, X128, X415, X416, X406, X407		
Echocardiography		3IP30	G560, G561, G562, G566, G567, G568, G570, G571, G572, G574, G575, G576, G577, G578, G581		
Holter Monitor		2HZ24JAKH	G311, G320, G647, G648, G649, G650, G651, G652, G653,		

			G654, G655, G656, G657, G658, G659, G660, G661, G682, G683, G684, G685, G686, G687, G688, G689, G690, G692, G693		
Cardiac Stress Test		2HZ08, 3IP70	G315, G174, G111, G112, G319, G582, G583, G584, J604, J606, J607, J608, J609, J611, J612, J613, J667, J807, J808, J809, J804, J811, J812, J813, J867, J666, J866		

Fecal Occult Blood Testing			Q043, Q150, Q152		
Prostate Specific Antigen			Q005, Q118, Q119, Q120, Q121, Q122, Q123, Q133		
Mammography			X172, X178, X184, X185, X201		
Influenza Vaccine			G590, G591		
Bone Mineral Density			J654, J688, J854, J888, X149, X152, X153, X155, Y654, Y688, Y854, Y888		
Chest X-ray			X090, X091, X092, X195		
Pulmonary Function Testing			J301, J303, J304, J305, J306, J307, J308, J309, J310, J311, J313, J315,		

			J316, J317, J318, J319, J320, J322, J323, J324, J327, J328, J330, J331, J332, J333, J334, J335, J340, J341, E450, E451		
Urine Albumin Creatinine Ratio					14959-1, 30000-4, 32294-1, XON10383-8, XON12394-3
Parathyroid Hormone					14866-8, 47178-9, 47093-0, 47180-5
Potassium					2823-3, 39789-3, 6298-4
Magnesium					2601-3
25-OH Hydroxy Vitamin D					14635-7
Phosphate					14879-1 24519-1

Appendix C.E- Inclusion and Exclusions of the study cohort



Appendix C.F- Baseline characteristics of new bisphosphonate users

New Bisphosphonate Users					
	All Patients N=56,847	**eGFR ≥60 mL/min/1.73m2 N=42,667**	**eGFR 30 - <60mL/min/1.73m2 N=13,390**	**eGFR 15 - <30 mL/min/1.73m2 N=705**	**eGFR <15 or chronic dialysis mL/min/1.73m2 N=85**
Demographics N (%)					
Mean Age (SD)	75.6 ± 7.3	74.2 ± 6.8	79.7 ± 7.4	81.2 ± 7.8	78.0 ± 7.3
Female	42,541 (74.8)	32,010 (75.0)	9,998 (74.7)	485 (68.8)	48 (56.5)
Fiscal year					
2011	54 (0.1)	31 (0.1)	23 (0.2)		0 (0.0)
2012	305 (0.5)	203 (0.5)	102 (0.7)		0 (0.0)
2013	1,404 (2.5)	1,098 (2.6)	289 (2.2)	17 (2.2)	
2014	5,456 (9.6)	4,246 (10.0)	1,131 (8.4)	79 (10.0)	
2015	7,220 (12.7)	5,538 (13.0)	1,583 (11.8)	89 (12.6)	10 (11.8)
2016	8,312 (14.6)	6,458 (15.1)	1,748 (13.1)	94 (13.3)	12 (14.1)
2017	9,474 (16.7)	6,904 (16.2)	2,434 (18.2)	122 (17.3)	14 (16.5)
2018	10,037 (17.7)	7,410 (17.4)	2,491 (18.6)	114 (16.2)	22 (25.9)
2019	11,702 (20.6)	8,695 (20.4)	2,845 (21.2)	146 (20.7)	16 (18.8)
2020	2,883 (5.1)	2,084 (4.9)	754 (5.6)	45 (5.7)	
Rural[a]	5,446 (9.6)	3,834 (9.0)	1,493 (11.2)	108 (15.3)	11 (12.9)
Long term Care	1,888 (3.3)	1,236 (2.9)	613 (4.6)	39 (4.9)	
Neighbourhood income quintile					
1 (lowest)	12,003 (21.1)	8,740 (20.5)	3,054 (22.8)	181 (25.5)	28 (32.9)
2	12,160 (21.4)	9,060 (21.2)	2,916 (21.8)	160 (22.7)	24 (28.2)

3	11,221 (19.7)	8,462 (19.8)	2,598 (19.4)	147 (20.9)	14 (16.5)
4	10,710 (18.8)	8,163 (19.1)	2,431 (18.2)	108 (15.3)	8 (9.4)
5 (highest)	10,636 (18.7)	8,159 (19.1)	2,357 (17.6)	109 (15.5)	11 (12.9)
Missing	117 (0.2)	83 (0.2)	34 (0.3)	* imputed as '1'	0 (0.0)
Dependency Quintile					
1 (lowest)	10,585 (18.6)	8,258 (19.4)	2,212 (16.5)	98 (13.9)	17 (20.0)
2	10,350 (18.2)	8,087 (19.0)	2,153 (16.1)	99 (14.0)	11 (12.9)
3	9,714 (17.1)	7,428 (17.4)	2,169 (16.2)	103 (14.6)	14 (16.5)
4	10,517 (18.5)	7,751 (18.2)	2,594 (19.4)	157 (22.3)	15 (17.6)
5 (highest)	15,423 (27.1)	10,955 (25.7)	4,199 (31.4)	269 (34.1)	
Missing	258 (0.5)	188 (0.4)	63 (0.5)	7 (0.9)	
Deprivation Quintile					
1 (lowest)	11,423 (20.1)	8,738 (20.5)	2,548 (19.0)	129 (18.3)	8 (9.4)
2	12,345 (21.7)	9,408 (22.0)	2,805 (20.9)	115 (16.3)	17 (20.0)
3	11,413 (20.1)	8,488 (19.9)	2,768 (20.7)	147 (20.9)	10 (11.8)
4	11,715 (20.6)	8,773 (20.6)	2,755 (20.6)	161 (22.8)	26 (30.6)
5 (highest)	9,693 (17.1)	7,072 (16.6)	2,451 (18.3)	170 (21.5)	
Missing	258 (0.5)	188 (0.4)	63 (0.5)	7 (0.9)	
Instability Quintile					
1 (lowest)	11,461 (20.2)	9,155 (21.5)	2,183 (16.3)	113 (16.0)	10 (11.8)
2	9,333 (16.4)	7,080 (16.6)	2,143 (16.0)	94 (13.3)	16 (18.8)
3	9,744 (17.1)	7,277 (17.1)	2,331 (17.4)	128 (18.2)	8 (9.4)
4	9,999 (17.6)	7,273 (17.0)	2,549 (19.0)	158 (22.4)	19 (22.4)
5 (highest)	16,052 (28.2)	11,694 (27.4)	4,121 (30.8)	237 (30.0)	
Missing	258 (0.5)	188 (0.4)	63 (0.5)	7 (0.9)	
Main Specialty of Prescriber					

Endocrinology	1,497 (2.6)	1,141 (2.7)	336 (2.5)	20 (2.5)	
GP/FP	42,481 (74.7)	32,189 (75.4)	9,753 (72.8)	483 (68.5)	56 (65.9)
Geriatric medicine	474 (0.8)	311 (0.7)	157 (1.2)	6 (0.9)	0 (0.0)
Internal medicine	856 (1.5)	632 (1.5)	205 (1.5)	19 (2.4)	
Nephrology	143 (0.3)	46 (0.1)	54 (0.4)	29 (4.1)	14 (16.5)
Rheumatology	2,970 (5.2)	2,194 (5.1)	733 (5.5)	43 (5.4)	
Other	1,593 (2.8)	1,144 (2.7)	411 (3.1)	32 (4.5)	6 (7.1)
Missing	6,833 (12.0)	5,010 (11.7)	1,741 (13.0)	82 (10.4)	
Comorbidities[b], N (%)					
Asthma	8,446 (14.9)	6,074 (14.2)	2,220 (16.6)	132 (18.7)	20 (23.5)
Arrhythmia	5,075 (8.9)	2,984 (7.0)	1,938 (14.5)	138 (19.6)	15 (17.6)
Chronic liver disease	2,673 (4.7)	2,045 (4.8)	590 (4.4)	38 (4.8)	
COPD	12,047 (21.2)	8,286 (19.4)	3,508 (26.2)	226 (32.1)	27 (31.8)
CHF	4,904 (8.6)	2,473 (5.8)	2,154 (16.1)	241 (34.2)	36 (42.4)
Acute Kidney Injury	1,789 (3.1)	551 (1.3)	1,022 (7.6)	189 (26.8)	27 (31.8)
Epilepsy	237 (0.4)	178 (0.4)	59 (0.4)		0 (0.0)
Coronary artery disease	10,086 (17.7)	6,524 (15.3)	3,308 (24.7)	234 (33.2)	20 (23.5)
Rheumatoid Arthritis	2,619 (4.6)	1,899 (4.5)	690 (5.2)	30 (3.8)	
IBD	540 (0.9)	379 (0.9)	145 (1.1)	16 (2.0)	
Other malabsorption syndrome	199 (0.4)	141 (0.3)	50 (0.4)	8 (1.0)	
Diabetes	15,865 (27.9)	10,830 (25.4)	4,621 (34.5)	374 (53.0)	40 (47.1)
Depression/Anxiety	4,916 (8.6)	3,521 (8.3)	1,327 (9.9)	60 (8.5)	8 (9.4)
Hypertension	39,124 (68.8)	27,274 (63.9)	11,119 (83.0)	653 (92.6)	78 (91.8)
Hypotension	1,013 (1.8)	562 (1.3)	402 (3.0)	49 (6.2)	
Parkinson	825 (1.5)	638 (1.5)	179 (1.3)	8 (1.1)	0 (0.0)
Thyrotoxicosis	1,526 (2.7)	1,122 (2.6)	379 (2.8)	25 (3.2)	

Hypothyroidism	808 (1.4)	499 (1.2)	285 (2.1)	24 (3.0)	
Hyperparathyroidism	99 (0.2)	54 (0.1)	45 (0.3)		0 (0.0)
Calcium deficiency	216 (0.4)	105 (0.2)	89 (0.7)	22 (2.4)	
Multiple Sclerosis	88 (0.2)	71 (0.2)	17 (0.1)	0 (0.0)	0 (0.0)
Vitamin D deficiency	35 (0.1)	21 (0.0)	14 (0.1)		0 (0.0)
Osteoporosis	17,500 (30.8)	13,798 (32.3)	3,528 (26.3)	154 (21.8)	20 (23.5)
Stroke/TIA	1,186 (2.1)	779 (1.8)	379 (2.8)	28 (3.5)	
Syncope	2,377 (4.2)	1,485 (3.5)	822 (6.1)	70 (8.9)	
dementia	5,003 (8.8)	3,133 (7.3)	1,764 (13.2)	95 (13.5)	11 (12.9)
Alcohol	311 (0.5)	238 (0.6)	67 (0.5)	6 (0.8)	
Lupus	43 (0.1)	25 (0.1)	18 (0.1)		
Fall	6,201 (10.9)	4,236 (9.9)	1,825 (13.6)	129 (18.3)	11 (12.9)
Fragility fractures	9,434 (16.6)	6,656 (15.6)	2,607 (19.5)	162 (23.0)	9 (10.6)
Charlson Comorbidity Index (SD)	0.69 ± 1.17	0.55 ± 1.02	0.97 ± 1.36	1.90 ± 1.78	2.82 ± 1.82
Medications[c] N (%)					
Aromatase inhibitors	13 (0.0)	8-12 (0.0)	<6 (0.0)	0 (0.0)	0 (0.0)
Proton pump inhibitors	15,310 (26.9)	10,162 (23.8)	4,781 (35.7)	329 (46.7)	38 (44.7)
Selective Serotonin Reuptake Inhibitors	6,152 (10.8)	4,277 (10.0)	1,767 (13.2)	98 (13.9)	10 (11.8)
Anticonvulsants	5,285 (9.3)	3,695 (8.7)	1,496 (11.2)	85 (12.1)	9 (10.6)
Anticoagulants	5,070 (8.9)	2,933 (6.9)	2,001 (14.9)	126 (17.9)	10 (11.8)
Calcitonin	10 (0.0)	10 (0.0)		0 (0.0)	0 (0.0)
Activated Vitamin D	198 (0.3)	88 (0.2)	52 (0.4)	35 (5.0)	23 (27.1)
Vitamin D	8 (0.0)	8 (0.0)		0 (0.0)	0 (0.0)
Loop diuretics	3,864 (6.8)	1,781 (4.2)	1,790 (13.4)	260 (36.9)	33 (38.8)
Thiazide diuretics	5,624 (9.9)	3,658 (8.6)	1,845 (13.8)	112 (15.9)	9 (10.6)

Thyroid replacement	9,672 (17.0)	6,564 (15.4)	2,910 (21.7)	180 (25.5)	18 (21.2)
Estrogen[d]	2,380 (4.2)	1,863 (4.4)	495 (3.7)	22 (3.1)	0 (0.0)
Denosumab [d]	337 (0.6)	242 (0.6)	85 (0.6)	10 (1.3)	
Intravenous bisphosphonate[d]	13 (0.0)	13 (0.0)		0 (0.0)	0 (0.0)
Oral steroid [d]	7,317 (12.9)	5,038 (11.8)	2,115 (15.8)	148 (21.0)	16 (18.8)
Inhaled steroid [d]	6,264 (11.0)	4,641 (10.9)	1,541 (11.5)	68 (9.6)	14 (16.5)
Antithyroid medication	115 (0.2)	82 (0.2)	33 (0.2)		0 (0.0)
Antihypertensive	32,785 (57.7)	22,309 (52.3)	9,809 (73.3)	596 (84.5)	71 (83.5)
Antiplatelet agents	2,525 (4.4)	1,552 (3.6)	894 (6.7)	79 (10.0)	
Benzodiazepine	5,345 (9.4)	3,774 (8.8)	1,480 (11.1)	76 (10.8)	15 (17.6)
Cholinesterase inhibitors	1,577 (2.8)	981 (2.3)	573 (4.3)	23 (2.9)	
Anti-arrhythmic	582 (1.0)	266 (0.6)	287 (2.1)	29 (3.7)	
Anticholinergics	2,667 (4.7)	1,821 (4.3)	784 (5.9)	52 (7.4)	10 (11.8)
Testosterone	85 (0.1)	57 (0.1)	28 (0.2)		
Insulin	1,902 (3.3)	1,033 (2.4)	740 (5.5)	115 (16.3)	14 (16.5)
Sulfonylurea	2,491 (4.4)	1,635 (3.8)	773 (5.8)	83 (10.5)	
Thiazolidinediones	45 (0.1)	23 (0.1)	22 (0.2)	0 (0.0)	0 (0.0)
Repaglinide	8 (0.0)	8 (0.0)			0 (0.0)
SGLT2 inhibitors	1,018 (1.8)	761 (1.8)	257 (1.8)		0 (0.0)
Metformin	7,536 (13.3)	5,370 (12.6)	2,089 (15.6)	77 (9.7)	
Mean number of medications (SD)	5.45 ± 4.32	4.91 ± 4.10	6.93 ± 4.48	9.40 ± 4.83	10.75 ± 5.20
Median Number of Medications (IQR)	5.00 (2.00-8.00)	4.00 (2.00-7.00)	6.00 (4.00-10.00)	9.00 (6.00-12.00)	11.00 (8.00-13.00)
Health Care Usage[e]					
Mean Number of Family Doctor Visits (SD)	10.08 ± 11.03	9.55 ± 10.57	11.51 ± 11.97	14.22 ± 15.40	12.67 ± 13.14

Median number of Family Doctor Visits (IQR)	7.00 (4.00-12.00)	7.00 (4.00-11.00)	8.00 (5.00-14.00)	9.00 (5.00-17.00)	8.00 (4.00-16.00)
Mean Number of Nephrologist Visits (SD)	0.20 ± 1.95	0.07 ± 0.70	0.31 ± 1.66	2.83 ± 8.32	24.36 ± 25.50
Median Number of Nephrologist Visits (IQR)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	1.00 (0.00-3.00)	8.00 (3.00-52.00)
Mean Number of Orthopedist Visits (SD)	0.82 ± 2.34	0.81 ± 2.32	0.87 ± 2.42	0.75 ± 1.92	1.04 ± 2.75
Mean Number of Endocrinologist Visits (SD)	0.18 ± 0.84	0.16 ± 0.75	0.23 ± 1.07	0.36 ± 1.27	0.44 ± 1.29
Mean Number of Endocrinologist Visits (SD)	1.78 ± 4.70	1.55 ± 4.25	2.33 ± 5.40	4.45 ± 9.03	9.62 ± 15.86
Median Number of Internist Visits (IQR)	0.00 (0.00-2.00)	0.00 (0.00-1.00)	1.00 (0.00-2.00)	2.00 (0.00-4.00)	3.00 (0.00-10.00)
Mean Number of Rheumatologist Visits (SD)	0.36 ± 1.54	0.34 ± 1.53	0.41 ± 1.60	0.39 ± 1.36	0.18 ± 0.60
Mean Number of Geriatric Visits (SD)	0.32 ± 2.32	0.29 ± 2.22	0.41 ± 2.60	0.40 ± 2.23	0.29 ± 1.53
Median Number of Geriatric Visits (IQR)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
Mean Number of hospitalizations (SD)	0.47 ± 0.96	0.43 ± 0.92	0.58 ± 1.04	0.86 ± 1.31	1.20 ± 1.40
Median Number of Hospitalizations (IQR)	0.00 (0.00-1.00)	0.00 (0.00-1.00)	0.00 (0.00-1.00)	0.00 (0.00-1.00)	1.00 (0.00-2.00)
Number of Hospitalizations					
0	40,004 (70.4)	30,889 (72.4)	8,682 (64.8)	396 (56.2)	37 (43.5)
1	10,740 (18.9)	7,686 (18.0)	2,880 (21.5)	155 (22.0)	19 (22.4)
2	3,967 (7.0)	2,718 (6.4)	1,157 (8.6)	78 (11.1)	14 (16.5)
3+	2,136 (3.8)	1,374 (3.2)	671 (5.0)	76 (10.8)	15 (17.6)
Mean Number of ER visits (SD)	0.60 ± 1.28	0.55 ± 1.20	0.74 ± 1.42	1.07 ± 2.39	1.14 ± 1.55

Median Number of ER visits (IQR)	0.00 (0.00-1.00)	0.00 (0.00-1.00)	0.00 (0.00-1.00)	0.00 (0.00-1.00)	1.00 (0.00-2.00)
Mean Number of serum creatinine tests (SD)	3.79 ± 5.46	3.31 ± 4.70	5.00 ± 6.75	9.02 ± 9.97	14.38 ± 12.26
Mean Number of serum calcium tests (SD)	0.87 ± 2.15	0.74 ± 1.79	1.14 ± 2.73	2.97 ± 4.29	8.16 ± 7.37
Number of serum calcium tests, N (%)	0.87 ± 2.15	0.74 ± 1.79	1.14 ± 2.73	2.97 ± 4.29	8.16 ± 7.37
0	33,261 (58.5)	26,103 (61.2)	6,980 (52.1)	178 (22.5)	
1-2	19,037 (33.5)	13,953 (32.7)	4,817 (36.0)	267 (33.8)	
3+	4,549 (8.0)	2,611 (6.1)	1,593 (11.9)	277 (39.3)	68 (80.0)
CT scan	13,665 (24.0)	9,421 (22.1)	3,974 (29.7)	238 (33.8)	32 (37.6)
Carotid ultrasound	2,608 (4.6)	1,772 (4.2)	780 (5.8)	56 (7.1)	
Echocardiography	11,954 (21.0)	8,099 (19.0)	3,587 (26.8)	233 (33.0)	35 (41.2)
Holter monitoring	5,085 (8.9)	3,512 (8.2)	1,500 (11.2)	73 (9.2)	
Cardiac stress test	4,918 (8.7)	3,680 (8.6)	1,173 (8.8)	57 (8.1)	8 (9.4)
Fecal occult blood test	56,731 (99.8)	42,575 (99.8)	13,366 (99.8)	705 (100.0)	85 (100.0)
Prostate-specific antigen test	3,376 (5.9)	2,914 (6.8)	441 (3.3)	21 (3.0)	0 (0.0)
Mammography	13,800 (24.3)	11,755 (27.6)	1,963 (14.7)	74 (10.5)	8 (9.4)
Influenza vaccination	20,560 (36.2)	15,023 (35.2)	5,213 (38.9)	296 (42.0)	28 (32.9)
Bone mineral density	29,425 (51.8)	22,745 (53.3)	6,376 (47.6)	268 (38.0)	36 (42.4)
Chest x-ray	21,883 (38.5)	15,321 (35.9)	6,123 (45.7)	386 (54.8)	53 (62.4)
Pulmonary function test	4,513 (7.9)	3,206 (7.5)	1,231 (9.2)	61 (8.7)	15 (17.6)
Laboratory Testing[f]					
Serum Calcium tested, N (%)	9,183 (16.2)	6,054 (14.2)	2,759 (20.6)	309 (43.8)	61 (71.8)
Corrected calcium (mmol/L) (SD)	2.35 ± 0.13	2.35 ± 0.12	2.37 ± 0.13	2.35 ± 0.15	2.35 ± 0.19
Ionized calcium tested, N (%)	2,363 (4.2)	1,691 (4.0)	619 (4.6)	46 (6.5)	7 (8.2)

Ionized calcium value (mmol/l) (SD)	1.24 ± 0.11	1.24 ± 0.10	1.24 ± 0.13	1.25 ± 0.14	1.15 ± 0.17
Urine ACR tested, N (%)	19,578 (34.4)	13,730 (32.2)	5,332 (39.8)	470 (66.7)	46 (54.1)
ACR value (mg/mmol) (SD)	7.35 ± 35.58	4.26 ± 23.50	11.39 ± 45.68	39.79 ± 88.19	133.24 ± 148.27
Serum potassium tested, N (%)	48,964 (86.1)	35,918 (84.2)	12,274 (91.7)	688 (97.6)	84 (98.8)
Serum potassium value (mmol/l) (SD)	4.37 ± 0.45	4.34 ± 0.44	4.43 ± 0.48	4.56 ± 0.53	4.67 ± 0.65
Serum magnesium tested, N (%)	13,385 (23.5)	9,016 (21.1)	3,976 (29.7)	335 (47.5)	58 (68.2)
Serum magnesium value (mmol/l) (SD)	0.83 ± 0.10	0.83 ± 0.10	0.83 ± 0.11	0.84 ± 0.13	0.88 ± 0.16
PTH tested, N (%)	5,484 (9.6)	3,620 (8.5)	1,541 (11.5)	258 (36.6)	65 (76.5)
PTH value (pmol/l)	7.08 ± 12.32	5.48 ± 3.55	7.45 ± 6.38	19.45 ± 41.91	38.01 ± 50.25
PTH Value (pmol/L)					
0 to 10	4,904 (8.6)	3,418 (8.0)	1,327 (9.9)	147 (20.9)	12 (14.1)
11 to 20	439 (0.8)	172 (0.4)	176 (1.3)	69 (9.8)	22 (25.9)
21 to 30	76 (0.1)	23 (0.1)	27 (0.2)	16 (2.3)	10 (11.8)
31 to 40	22 (0.0)	11 (0.0)		11 (1.4)	
41 to 50	10 (0.0)	<6 (0.0)	0 (0.0)	<6 (<0.9)	<6 (<7.1)
>50	33 (0.1)	20 (0.0)			13 (15.3)
Missing	51,363 (90.4)	39,047 (91.5)	11,849 (88.5)	447 (63.4)	20 (23.5)
Vitamin D tested, N (%)	14,507 (25.5)	10,941 (25.6)	3,373 (25.2)	170 (24.1)	23 (27.1)
Vitamin D value (nmol/L) (SD)	81.20 ± 35.19	81.05 ± 35.07	81.99 ± 35.68	75.14 ± 32.38	77.83 ± 35.08
Phosphate tested, N (%)	12,244 (21.5)	7,848 (18.4)	3,853 (28.8)	467 (66.2)	76 (89.4)
Phosphate value (mmol/L) (SD)	1.11 ± 0.20	1.10 ± 0.19	1.10 ± 0.20	1.18 ± 0.24	1.52 ± 0.37

Cell counts (i.e. <=5) are suppressed as per ICES privacy policies

[a] Rural defined as residing in a location with a population of ≤ 10 000 individuals.

[b] Comorbidities in the 5 years prior to the index prescription date were considered.
[c] Medication use in the 120 days (unless otherwise specified) prior to index prescription date were considered. There were no prescriptions for cinacalcet.
[d] Concurrent medication use in the 365 days prior to index prescription date were considered
[e] Health care contacts in the 365 days prior to index prescription date were considered.
[f] Laboratory measurements in the 365 days prior to index prescription date were considered.

Abbreviations: eGFR, estimated glomerular filtration rate; SD, standard deviation; GP/FP, general practitioner/family practitioner COPD, Chronic Obstructive Pulmonary Disease; CHF, Congestive Heart Failure; IBD, Inflammatory Bowel Disease; SGLT-2, sodium glucose co-transporter-2; ER, Emergency Room; ACR, albumin to creatinine ratio; PTH, parathyroid hormone; TIA, transient ischemic attack
The most recent eGFR measurement in the 365-day period before the cohort entry date (including the cohort entry date); eGFR was calculated using the Chronic Kidney Disease (CKD)–Epidemiology (EPI) equation: $141 \times \min([\text{serum creatinine concentration in } \mu\text{mol/L}/88.4]/\kappa, 1)^{\alpha} \times \max([\text{serum creatinine concentration in } \mu\text{mol/L}/88.4]/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018$ [if female] × 1.159 [if African-American]; κ=0.7 if female and 0.9 if male; α=-0.329 if female and -0.411 if male; min=the minimum of serum creatinine concentration/κ or 1; max=the maximum of serum creatinine concentration/κ or 1. Information on race was not available in our data sources and all patients were assumed not to be of African-Canadian race; African-Canadians represented less than 5% of the population of Ontario in 2006.

Appendix C.G- Baseline characteristics of new denosumab users

New Denosumab Users					
	All Patients N=59, 151	**eGFR ≥60 mL/min/1.73m^2 N=39,742**	**eGFR 30 - <60 mL/min/1.73m^2 N=17,376**	**eGFR 15 - <30 mL/min/1.73m^2 N=1,859**	**eGFR <15 mL/min/1.73m^2 or chronic dialysis N=174**
Demographics, N (%)					
Mean Age (SD)	79.3 ± 8.1	79.3 ± 8.1	79.3 ± 8.1	79.3 ± 8.1	79.2 ± 7.7
Female	53,339 (90)	36,058 (91)	15,520 (89)	1,620 (87)	141 (81)
Fiscal year					
2011	148 (0.2)	102 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
2012			46 (0.3)	0 (0.0)	0 (0.0)
2013	1,022 (1.7)	699 (1.8)	286 (1.6)	37 (1.8)	
2014	5,288 (8.9)	3,699 (9.3)	1,442 (8.3)	147 (7.2)	
2015	7,065 (11.9)	4,919 (12.4)	1,951 (11.2)	180 (9.7)	15 (8.6)
2016	8,030 (13.6)	5,585 (14.1)	2,192 (12.6)	228 (12.3)	25 (14.4)
2017	8,879 (15.0)	5,668 (14.3)	2,860 (16.5)	324 (17.4)	27 (15.5)
2018	12,429 (21.0)	8,210 (20.7)	3,762 (21.7)	422 (22.7)	35 (20.1)
2019	13,113 (22.2)	8,775 (22.1)	3,889 (22.4)	414 (22.3)	35 (20.1)
2020	3,177 (5.4)	2,085 (5.2)	948 (5.5)	127 (6.8)	17 (9.8)
Rural[a]	3,911 (6.6)	2,497 (6.3)	1,240 (7.1)	160 (8.6)	14 (8.0)
Long term Care	8,680 (14.7)	4,582 (11.5)	3,612 (20.8)	453 (24.4)	33 (19.0)
Neighbourhood income quintile					
1 (lowest)	13,968 (23.6)	8,972 (22.6)	4,425 (25.5)	511 (27.5)	60 (34.5)
2	12,504 (21.1)	8,245 (20.7)	3,799 (21.9)	412 (22.2)	48 (27.6)
3	10,568 (17.9)	7,174 (18.1)	3,046 (17.5)	321 (17.3)	27 (15.5)

4	10,629 (18.0)	7,288 (18.3)	2,999 (17.3)	320 (17.2)	22 (12.6)
5 (highest)	11,305 (19.1)	7,965 (20.0)	3,037 (17.5)	286 (15.4)	17 (9.8)
Missing	177 (0.3)	98 (0.2)	70 (0.4)	9 (0.5)	0 (0.0)
Dependency Quintile					
1 (lowest)	9,234 (15.6)	6,541 (16.5)	2,412 (13.9)	258 (13.9)	23 (13.2)
2	9,751 (16.5)	6,833 (17.2)	2,606 (15.0)	280 (15.1)	32 (18.4)
3	9,566 (16.2)	6,581 (16.6)	2,675 (15.4)	284 (15.3)	26 (14.9)
4	11,067 (18.7)	7,453 (18.8)	3,251 (18.7)	330 (17.8)	33 (19.0)
5 (highest)	19,290 (32.6)	12,196 (30.7)	6,342 (36.5)	692 (37.2)	60 (34.5)
Missing	243 (0.4)	138 (0.3)	90 (0.5)	15 (0.8)	0 (0.0)
Deprivation Quintile					
1 (lowest)	12,482 (21.1)	8,670 (21.8)	3,463 (19.9)	321 (17.3)	28 (16.1)
2	12,542 (21.2)	8,625 (21.7)	3,521 (20.3)	375 (20.2)	21 (12.1)
3	11,275 (19.1)	7,626 (19.2)	3,261 (18.8)	357 (19.2)	31 (17.8)
4	12,227 (20.7)	8,018 (20.2)	3,775 (21.7)	391 (21.0)	43 (24.7)
5 (highest)	10,382 (17.6)	6,665 (16.8)	3,266 (18.8)	400 (21.5)	51 (29.3)
Missing	243 (0.4)	138 (0.3)	90 (0.5)	15 (0.8)	0 (0.0)
Instability Quintile					
1 (lowest)	10,129 (17.1)	7,441 (18.7)	2,430 (14.0)	230 (12.4)	28 (16.1)
2	9,104 (15.4)	6,310 (15.9)	2,507 (14.4)	268 (14.4)	19 (10.9)
3	9,319 (15.8)	6,306 (15.9)	2,697 (15.5)	298 (16.0)	18 (10.3)
4	10,978 (18.6)	7,004 (17.6)	3,563 (20.5)	376 (20.2)	35 (20.1)
5 (highest)	19,378 (32.8)	12,543 (31.6)	6,089 (35.0)	672 (36.1)	74 (42.5)
Missing	243 (0.4)	138 (0.3)	90 (0.5)	15 (0.8)	0 (0.0)
Main Specialty of Prescriber					
Endocrinology	3,727 (6.3)	2,627 (6.6)	966 (5.6)	121 (6.5)	13 (7.5)

GP/FP	45,942 (77.7)	30,755 (77.4)	13,641 (78.5)	1,421 (76.4)	125 (71.8)
Geriatric medicine	1,648 (2.8)	1,136 (2.9)	466 (2.7)	46 (2.3)	
Internal medicine	734 (1.2)	487 (1.2)	218 (1.3)	29 (1.4)	
Nephrology	46 (0.1)	23 (0.1)	12 (0.1)	11 (0.5)	
Rheumatology	2,940 (5.0)	2,097 (5.3)	761 (4.4)	68 (3.7)	14 (8.0)
Other	1,238 (2.1)	816 (2.1)	373 (2.1)	49 (2.4)	
Missing	2,876 (4.9)	1,801 (4.5)	939 (5.4)	124 (6.7)	12 (6.9)
Comorbidities[b], N (%)					
Asthma	10,186 (17.2)	6,646 (16.7)	3,165 (18.2)	345 (18.6)	30 (17.2)
Arrhythmia	6,732 (11.4)	3,284 (8.3)	2,957 (17.0)	449 (24.2)	42 (24.1)
Chronic liver disease	2,827 (4.8)	1,980 (5.0)	745 (4.3)	81 (4.4)	21 (12.1)
COPD	13,769 (23.3)	8,384 (21.1)	4,744 (27.3)	593 (31.9)	48 (27.6)
CHF	7,076 (12.0)	2,963 (7.5)	3,345 (19.3)	686 (36.9)	82 (47.1)
Acute Kidney Injury	2,949 (5.0)	668 (1.7)	1,688 (9.7)	518 (27.9)	75 (43.1)
Epilepsy	254 (0.4)	187 (0.5)	61 (0.4)	6 (0.3)	0 (0.0)
Coronary artery disease	10,715 (18.1)	5,955 (15.0)	4,104 (23.6)	599 (32.2)	57 (32.8)
Rheumatoid Arthritis	3,365 (5.7)	2,229 (5.6)	1,025 (5.9)	103 (5.5)	8 (4.6)
IBD	715 (1.2)	474 (1.2)	207 (1.2)	34 (1.7)	
Other malabsorption syndrome	265 (0.4)	201 (0.5)	64 (0.3)		0 (0.0)
Diabetes	16,084 (27.2)	9,491 (23.9)	5,539 (31.9)	943 (50.7)	111 (63.8)
Depression/Anxiety	6,328 (10.7)	4,048 (10.2)	2,037 (11.7)	222 (11.9)	21 (12.1)
Hypertension	44,482 (75.2)	27,541 (69.3)	15,000 (86.3)	1,776 (95.5)	165 (94.8)
Hypotension	1,572 (2.7)	808 (2.0)	645 (3.7)	101 (5.4)	18 (10.3)
Parkinson	1,243 (2.1)	900 (2.3)	319 (1.8)	24 (1.2)	
Thyrotoxicosis	1,806 (3.1)	1,230 (3.1)	521 (3.0)	55 (2.7)	

Hypothyroidism	1,443 (2.4)	762 (1.9)	585 (3.4)	89 (4.8)	7 (4.0)
Hyperparathyroidism	159 (0.3)	71 (0.2)	69 (0.4)	19 (0.9)	
Calcium deficiency	289 (0.5)	113 (0.3)	139 (0.8)	26 (1.4)	11 (6.3)
Multiple Sclerosis	151 (0.3)	127 (0.3)	24 (0.1)		
Vitamin D deficiency	47 (0.1)	26 (0.1)	21 (0.1)		0 (0.0)
Osteoporosis	32,229 (54.5)	23,212 (58.4)	8,228 (47.4)	720 (38.7)	69 (39.7)
Stroke/TIA	1,564 (2.6)	900 (2.3)	591 (3.4)	73 (3.6)	
Syncope	3,473 (5.9)	1,921 (4.8)	1,377 (7.9)	158 (8.5)	17 (9.8)
dementia	12,238 (20.7)	6,586 (16.6)	5,023 (28.9)	590 (31.7)	39 (22.4)
Alcohol	216 (0.4)	136 (0.3)	71 (0.4)	9 (0.5)	0 (0.0)
Lupus	60 (0.1)	39 (0.1)	21 (0.1)		0 (0.0)
Fall	9,821 (16.6)	5,762 (14.5)	3,532 (20.3)	481 (25.9)	46 (26.4)
Fragility fractures	13,971 (23.6)	8,705 (21.9)	4,647 (26.7)	565 (30.4)	54 (31.0)
Charlson Comorbidity Index	0.78 ± 1.22	0.56 ± 0.99	1.02 ± 1.35	2.06 ± 1.78	3.21 ± 1.81
Medication Use[c], N (%)					
Aromatase inhibitors	6 (0.0)	<6	<6	0 (0.0)	0 (0.0)
Proton pump inhibitors	20,602 (34.8)	12,262 (30.9)	7,315 (42.1)	933 (50.2)	92 (52.9)
Selective Serotonin Reuptake Inhibitors	8,949 (15.1)	5,397 (13.6)	3,202 (18.4)	320 (17.2)	30 (17.2)
Anticonvulsants	6,626 (11.2)	4,161 (10.5)	2,181 (12.6)	261 (14.0)	23 (13.2)
Anticoagulants	6,916 (11.7)	3,373 (8.5)	3,103 (17.9)	413 (22.2)	27 (15.5)
Calcitonin	20 (0.0)	13 (0.0)	7 (0.0)	0 (0.0)	0 (0.0)
Activated Vitamin D	572 (1.0)	217 (0.5)	193 (1.1)	108 (5.8)	54 (31.0)
Vitamin D	13 (0.0)	7 (0.0)	6 (0.0)		0 (0.0)
Loop diuretics	5,896 (10.0)	2,153 (5.4)	2,960 (17.0)	707 (38.0)	76 (43.7)
Thiazide diuretics	5,262 (8.9)	3,051 (7.7)	1,955 (11.3)	245 (13.2)	11 (6.3)

Thyroid replacement	12,925 (21.9)	7,853 (19.8)	4,454 (25.6)	569 (30.6)	49 (28.2)
Estrogen[e]	3,198 (5.4)	2,339 (5.9)	801 (4.6)	58 (2.9)	
Oral bisphosphonate[d]	30,883 (52.2)	20,937 (52.7)	9,094 (52.3)	801 (43.1)	51 (29.3)
Intravenous bisphosphonate[d]	97 (0.2)	70 (0.2)	27 (0.1)		0 (0.0)
Oral steroid[e]	5,821 (9.8)	3,522 (8.9)	2,000 (11.5)	272 (14.6)	27 (15.5)
Inhaled steroid[e]	7,253 (12.3)	4,892 (12.3)	2,138 (12.3)	205 (11.0)	18 (10.3)
Antithyroid medication	148 (0.3)	95 (0.2)	53 (0.3)		0 (0.0)
Antihypertensive	36,714 (62.1)	22,072 (55.5)	12,897 (74.2)	1,600 (86.1)	145 (83.3)
Androgen deprivation	17 (0.0)	9 (0.0)	8 (0.0)	0 (0.0)	0 (0.0)
Antiplatelet agents	2,927 (4.9)	1,507 (3.8)	1,203 (6.9)	196 (10.5)	21 (12.1)
Benzodiazepine	7,081 (12.0)	4,535 (11.4)	2,306 (13.3)	216 (11.6)	24 (13.8)
Cholinesterase inhibitors	4,001 (6.8)	2,097 (5.3)	1,710 (9.8)	187 (10.1)	7 (4.0)
Anti-arrhythmic	699 (1.2)	249 (0.6)	380 (2.2)	61 (3.3)	9 (5.2)
Anticholinergics	3,023 (5.1)	1,803 (4.5)	1,047 (6.0)	160 (8.6)	13 (7.5)
Testosterone	55 (0.1)	37 (0.1)	18 (0.1)		
Insulin	2,029 (3.4)	834 (2.1)	858 (4.9)	291 (15.7)	46 (26.4)
Sulfonylurea	2,058 (3.5)	1,132 (2.8)	744 (4.3)	173 (9.3)	9 (5.2)
Thiazolidinediones	48 (0.1)	27 (0.1)	21 (0.1)		
Repaglinide	7 (0.0)	<6	<6	<6	0 (0.0)
SGLT2 inhibitors	795 (1.3)	529 (1.3)	244 (1.4)	22 (1.1)	
Metformin	6,259 (10.6)	4,048 (10.2)	2,047 (11.8)	164 (8.1)	
Health Care Use[e]					
Mean number of medications (SD)	7.05 ± 4.75	6.26 ± 4.49	8.42 ± 4.77	10.68 ± 5.10	11.59 ± 4.57
Median Number of Medications (IQR)	6.00 (3.00-10.00)	5.00 (3.00-9.00)	8.00 (5.00-11.00)	10.00 (7.00-14.00)	11.00 (8.00-15.00)

Mean Number of Family Doctor Visits (SD)	12.00 ± 12.69	11.19 ± 11.84	13.36 ± 13.73	16.24 ± 16.54	18.11 ± 19.78
Median number of Family Doctor Visits (IQR)	8.00 (5.00-14.00)	8.00 (5.00-13.00)	10.00 (5.00-16.00)	12.00 (6.00-19.00)	12.00 (7.00-20.00)
Mean Number of Nephrologist Visits (SD)	0.27 ± 2.50	0.10 ± 1.41	0.30 ± 1.59	1.75 ± 5.55	20.21 ± 25.97
Median Number of Nephrologist Visits (IQR)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	1.00 (0.00-2.00)	5.00 (2.00-48.00)
Mean Number of Orthopedist Visits (SD)	0.87 ± 2.35	0.87 ± 2.36	0.85 ± 2.31	0.97 ± 2.61	1.01 ± 2.22
Mean Number of Endocrinologist Visits (SD)	0.25 ± 1.00	0.23 ± 0.95	0.25 ± 1.04	0.46 ± 1.26	0.80 ± 1.96
Mean Number of Endocrinologist Visits (SD)	2.15 ± 5.72	1.81 ± 5.16	2.60 ± 6.18	4.32 ± 8.67	11.27 ± 15.20
Median Number of Internist Visits (IQR)	0.00 (0.00-2.00)	0.00 (0.00-2.00)	1.00 (0.00-2.00)	1.00 (0.00-5.00)	5.00 (1.00-16.00)
Mean Number of Rheumatologist Visits (SD)	0.41 ± 1.58	0.41 ± 1.61	0.40 ± 1.51	0.41 ± 1.62	0.36 ± 1.40
Mean Number of Geriatric Visits (SD)	0.40 ± 2.39	0.34 ± 2.19	0.50 ± 2.57	0.79 ± 4.02	0.52 ± 2.15
Mean Number of hospitalizations (SD)	0.50 ± 0.97	0.46 ± 0.91	0.57 ± 1.04	0.82 ± 1.29	1.21 ± 1.62
Median Number of Hospitalizations (IQR)	0.00 (0.00-1.00)	0.00 (0.00-1.00)	0.00 (0.00-1.00)	0.00 (0.00-1.00)	1.00 (0.00-2.00)
Number of Hospitalizations					
0	40,314 (68.2)	27,936 (70.3)	11,283 (64.9)	1,020 (54.9)	75 (43.1)
1	12,155 (20.5)	7,826 (19.7)	3,815 (22.0)	461 (24.8)	53 (30.5)
2	4,332 (7.3)	2,675 (6.7)	1,427 (8.2)	213 (11.5)	17 (9.8)
3+	2,350 (4.0)	1,305 (3.3)	851 (4.9)	165 (8.9)	29 (16.7)
Mean Number of ER visits (SD)	0.64 ± 1.24	0.59 ± 1.20	0.73 ± 1.29	0.87 ± 1.39	1.04 ± 1.63

Median Number of ER visits (IQR)	0.00 (0.00-1.00)	0.00 (0.00-1.00)	0.00 (0.00-1.00)	0.00 (0.00-1.00)	1.00 (0.00-1.00)
Mean Number of serum creatinine tests (SD)	4.44 ± 6.06	3.74 ± 5.12	5.38 ± 6.64	9.49 ± 10.56	16.14 ± 17.20
Mean Number of serum calcium tests (SD)	1.24 ± 2.45	1.03 ± 2.10	1.43 ± 2.56	3.04 ± 4.32	9.11 ± 8.68
Number of serum calcium tests, N (%)					
0	25,477 (43.1)	18,413 (46.3)	6,694 (38.5)	362 (19.5)	8 (4.6)
1-2	26,121 (44.2)	17,581 (44.2)	7,809 (44.9)	708 (38.1)	23 (13.2)
3+	7,553 (12.8)	3,748 (9.4)	2,873 (16.5)	789 (42.4)	143 (82.2)
CT scan	15,970 (27.0)	9,824 (24.7)	5,423 (31.2)	651 (35.0)	72 (41.4)
Carotid ultrasound	2,507 (4.2)	1,559 (3.9)	825 (4.7)	105 (5.6)	18 (10.3)
Echocardiography	11,978 (20.2)	7,250 (18.2)	4,072 (23.4)	592 (31.8)	64 (36.8)
Holter monitoring	5,224 (8.8)	3,262 (8.2)	1,754 (10.1)	192 (10.3)	16 (9.2)
Cardiac stress test	4,023 (6.8)	2,819 (7.1)	1,075 (6.2)	107 (5.8)	22 (12.6)
Fecal occult blood test	59,085 (99.9)	39,701 (99.9)	17,355 (99.9)	1,855 (99.8)	174 (100.0)
Prostate-specific antigen test	2,314 (3.9)	1,946 (4.9)	340 (2.0)	28 (1.4)	
Mammography	11,607 (19.6)	9,654 (24.3)	1,826 (10.5)	110 (5.9)	17 (9.8)
Influenza vaccination	24,341 (41.2)	16,603 (41.8)	6,963 (40.1)	713 (38.4)	62 (35.6)
Bone mineral density	31,498 (53.3)	23,008 (57.9)	7,783 (44.8)	653 (35.1)	54 (31.0)
Chest x-ray	25,762 (43.6)	15,795 (39.7)	8,746 (50.3)	1,101 (59.2)	120 (69.0)
Pulmonary function test	4,294 (7.3)	2,861 (7.2)	1,272 (7.3)	144 (7.7)	17 (9.8)
Laboratory Testing[f]					
Serum Calcium tested, N (%)	12,730 (21.5)	7,494 (18.9)	4,350 (25.0)	780 (42.0)	106 (60.9)
Corrected calcium (mmol/L) (SD)	2.35 ± 0.12	2.34 ± 0.12	2.36 ± 0.13	2.37 ± 0.15	2.37 ± 0.16
Ionized calcium tested, N (%)	4,323 (7.3)	2,844 (7.2)	1,265 (7.3)	190 (10.2)	24 (13.8)

Ionized calcium value (mmol/l) (SD)	1.24 ± 0.10	1.24 ± 0.08	1.25 ± 0.11	1.24 ± 0.11	1.18 ± 0.22
Urine Albumin to Creatinine Ratio tested, N (%)	18,412 (31.1)	11,482 (28.9)	5,761 (33.2)	1,069 (57.5)	100 (57.5)
ACR value (mg/mmol) (SD)	9.03 ± 38.99	3.75 ± 16.05	11.49 ± 43.32	41.82 ± 90.25	122.99 ± 165.62
Serum potassium tested , N (%)	51,841 (87.6)	33,816 (85.1)	16,018 (92.2)	1,834 (98.7)	173 (99.4)
Serum potassium value (mmol/l) (SD)	4.36 ± 0.45	4.32 ± 0.43	4.41 ± 0.47	4.60 ± 0.53	4.63 ± 0.67
Serum magnesium tested, N (%)	18,416 (31.1)	11,131 (28.0)	6,250 (36.0)	919 (49.4)	116 (66.7)
Serum magnesium value (mmol/l) (SD)	0.84 ± 0.10	0.84 ± 0.09	0.83 ± 0.11	0.86 ± 0.13	0.85 ± 0.16
PTH tested, N (%)	9,797 (16.6)	6,087 (15.3)	2,894 (16.7)	686 (36.9)	130 (74.7)
PTH value (pmol/l)	6.50 ± 7.10	5.09 ± 2.65	7.02 ± 5.60	11.89 ± 10.84	32.45 ± 35.19
PTH Value (pmol/L)					
0 to 10	8,863 (15.0)	5,888 (14.8)	2,513 (14.5)	429 (23.1)	33 (19.0)
11 to 20	727 (1.2)	187 (0.5)	318 (1.8)	185 (10.0)	37 (21.3)
21 to 30	110 (0.2)	48 (0.1)		43 (2.3)	19 (10.9)
31 to 40	39 (0.1)	18 (0.3)		12 (0.7)	9 (5.2)
41 to 50	15 (0.0)	9 (0.2)			6 (3.5)
>50	43 (0.1)	0 (0.0)	6 (0.0)	11 (0.6)	26 (14.9)
Missing	49,354 (83.4)	33,655 (84.7)	14,482 (83.3)	1,173 (63.1)	44 (25.3)
Vitamin D tested, N (%)	22,370 (37.8)	15,493 (39.0)	6,174 (35.5)	651 (35.0)	52 (29.9)
Vitamin D value (nmol/L) (SD)	91.47 ± 33.80	91.46 ± 34.00	91.74 ± 33.63	90.50 ± 30.17	72.94 ± 30.81
Phosphate tested, N (%)	17,738 (30.0)	10,353 (26.1)	6,005 (34.6)	1,218 (65.5)	162 (93.1)
Phosphate value (mmol/L) (SD)	1.13 ± 0.20	1.12 ± 0.19	1.12 ± 0.20	1.21 ± 0.21	1.44 ± 0.36

Cell counts (i.e. <=5) are suppressed as per ICES privacy policies

[a] Rural defined as residing in a location with a population of ≤ 10 000 individuals.
[b] Comorbidities in the 5 years prior to the index prescription date were considered.
[c] Medication use in the 120 days (unless otherwise specified) prior to index prescription date were considered. There were no prescriptions for cinacalcet.
[d] Concurrent medication use in the 365 days prior to index prescription date were considered
[e] Health care contacts in the 365 days prior to index prescription date were considered.
[f] Laboratory measurements in the 365 days prior to index prescription date were considered.

Abbreviations: eGFR, estimated glomerular filtration rate; SD, standard deviation; GP/FP, general practitioner/family practitioner COPD, Chronic Obstructive Pulmonary Disease; CHF, Congestive Heart Failure; IBD, Inflammatory Bowel Disease; SGLT-2, sodium glucose co-transporter-2; ER, Emergency Room; ACR, albumin to creatinine ratio; PTH, parathyroid hormone; TIA, transient ischemic attack
The most recent eGFR measurement in the 365-day period before the cohort entry date (including the cohort entry date); eGFR was calculated using the Chronic Kidney Disease (CKD)–Epidemiology (EPI) equation: $141 \times \min([\text{serum creatinine concentration in } \mu\text{mol/L}/88.4]/\kappa, 1)^{\alpha} \times \max([\text{serum creatinine concentration in } \mu\text{mol/L}/88.4]/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018$ [if female] × 1.159 [if African-American]; κ=0.7 if female and 0.9 if male; α=-0.329 if female and -0.411 if male; min=the minimum of serum creatinine concentration/κ or 1; max=the maximum of serum creatinine concentration/κ or 1. Information on race was not available in our data sources and all patients were assumed not to be of African-Canadian race; African-Canadians represented less than 5% of the population of Ontario in 2006.

Appendix C.H- Prescription characteristics

	Denosumab	**Bisphosphonates**
Median continuous use (days) [IQR]	456 [100-933]	218 [45-624]
Reasons for medication discontinuation at 365 days		
Death n (%)	544 (0.9%)	824 (1.5%)
Medication stop n (%)	19,573 (33.1%)	32,195 (56.6%)
Medication Switch n (%)	3,076 (5.2%)	326 (0.6%)

Appendix C.I- The incidence of calcium testing and hypocalcemia after denosumab and bisphosphonates

		Denosumab		Bisphosphonates	
Calcium Outcome	eGFR Category	n events/N Patients	Cumulative Incidence Rate (95% CI)	n events/N Patients	Cumulative Incidence Rates (95% CI)
Calcium Tested	All Patients	18,825/59,151	31.8 (31.5, 32.2)	12,777/56,847	22.5 (22.1, 22.8)
	eGFR ≥60	10,821/39,742	27.2 (26.8, 27.7)	8,371/42,667	19.6 (19.2, 20.0)
	eGFR 30 - <60	6,606/17,376	38.0 (37.3, 38.7)	3,895/13,390	29.1 (28.3, 29.9)
	eGFR 15- <30	1,237/1,859	66.5 (64.4-68.6)	511/790*	64.7 (61.3-67.9)
	eGFR <15 or maintenance dialysis	161/174	92.5 (87.3-96.7)		
Calcium <2.00 mmol/L	All Patients	369/59,151	0.62 (0.56, 0.69)	167/56,847	0.29 (0.25-0.34)
	eGFR ≥60	143/39,742	0.36 (0.31, 0.42)	99/42,667	0.23 (0.19-0.28)
	eGFR 30 - <60	119/17,376	0.69 (0.57, 0.82)	49/13,390	0.37 (0.28-0.48)
	eGFR 15- <30	65/1,859	3.5 (2.7, 4.4)	19/790*	2.40 (1.5-3.7)
	eGFR <15 or maintenance dialysis	42/1,859	24.1 (18.1, 30.7)		
Calcium <1.80 mmol/L	All Patients	129/59,151	0.22 (0.18, 0.26)	50/56,847	0.09 (0.07-0.12)
	eGFR ≥60	33/39,742	0.08 (0.06, 0.12)	29/42,667	0.07 (0.05-0.10)
	eGFR 30 - <60	41/17,376	0.24 (0.17, 0.32)	21/14,180*	0.12 (0.07-0.19)
	eGFR 15- <30	29/1,859	1.56 (2.07-2.20)		
	eGFR <15 or maintenance dialysis	26/174	14.9 (10.1-20.7)		

*cells combined due to low event numbers

Appendix C.J- rates of hypocalcemia in studies of denosumab in CKD

Author	Population	Definition	Incidence
Hiramatsu et al 2021[43]	Prospective cohort of HD Patients	<2.0 mmol/L	12/47 patients (25.5%)
Kunizawa et al 2020[44]	Prospective cohort of CKD and hemodialysis patients	2.0-2.12 mmol/L	4/79 CKD 3 patients (5%) 5/20 CKD 4,5 patients (25%) 21/121 HD patients (17%)
		1.75-1.99 mmol/L	0/79 CKD 3 patients (0%) 0/25 CKD4,5 patients (0%) 22/121 HD patients (18%)
		<1.75mmol/L	0/79 CKD 3 patients (0%) 1/20 CKD 4,5 patients (5%) 0/121 HD patients (0%)
Dave et al 2015[17]	Retrospective cohort of CKD and HD patients	1.75-2 mmol/L	1/7 HD patients (14.3%) 0/7 CKD 4,5 patients (0%)
		<1.75 mmol/L	4/7 HD patients (57.1%) 3/7 CKD 4,5 patients (42.9%)
Chen et al 2014[45]	Prospective cohort of 12 HD patients with severe hyperparathyroid	1.75-2mmol/L	2/12 (16.7%)
		<1.75 mmol/L	4/12 (33.3%)
		1.9-2 mmol/L	7/55 (12.7%)

Block et al 2012[8]	Prospective cohort of 55 patients ranging from normal renal function to HD	<1.9mmol/L	5/55 (9.0%)
Block et al 2014*[46]	Prospective cohort study of 32 CKD patients with malignancy	<1.75mmol/L	3/16 CKD 4 patients (18.8%) 10/16 CKD 5 patients (62.5%)
Hiramatsu et al 2015[47]	Prospective cohort of 11 HD patients	<2 mmol/L	4/11 (36.3%)
Chen et al 2015[45]	Prospective cohort of 24 HD patients with severe hyperparathyroidism	1.75-2.0 mmol/L	6/24 (25%)
		1.62-1.75 mmol/L	2/24 (8.3%)

*Patients received 120mg subcutaneous every 28 days apart then q12 weeks ongoing

Curriculum Vitae

Andrea Cowan

Education

Masters of Clinical Epidemiology and Biostatistics
September 2020-Present
University of Western Ontario, *London ON*

Clinical Fellow, London Health Sciences Centre
July 2021-June 2023
Schulich School of Medicine and Dentistry, *London ON*

Home Dialysis Fellowship
July 2020- June 2021
University of Western Ontario, *London ON*

Nephrology Fellowship
July 2018- June 2020
University of Western Ontario, *London ON*

Internal Medicine Residency
July 2015- June 2018
University of Western Ontario, *London ON*

Medical Doctorate
2011-2015
University of Western Ontario, *London ON*

Bachelor of Science, Subject of Specialization in Biochemistry
2007- 2011
Queen's University*, Kingston ON*

Awards

2023- American Society of Bone and Mineral Research Young Investigator Award- $1000

2022-2023- Department of Medicine Resident Research Fellowship Program-$75,000 over 1 year

2021-2023- Clinician Investigator Program

2020- PSI Foundation Research Trainee Fellowship- $50,000 over two years

2019-2020 Chief Nephrology Resident

2018- Lloyd B Hession award for the PGY-3 who demonstrates exceptional ability in leadership, education, and high academic standing

2018- London Health Sciences Centre President's Award for Innovation for the design and implementation of a Patient-Oriented Discharge Summary

2017-2018 Chief Resident- Internal Medicine

2016- Nominee: Class of '49 Award for Excellence in Teaching by Residents

2011- Dean's Honour List Queen's University

2011- Society of Chemical Industry Student Merit Award: Awarded to the graduating biochemistry student with the highest GPA

Medical Licensure

Independent License College of the Physicians and Surgeons of Ontario, 2020- Present

Examinations

Medical Council of Canada Part I and II, 2016
The Royal College of Physicians and Surgeons of Canada, Specialty in Internal Medicine, 2019
The Royal College of Physicians and Surgeons of Canada, Specialty in Nephrology, 2020

Administrative and Teaching Activities

Canadian Resuscitative Ultrasound Course: Vascular Access
2022

Internal Medicine Half Day
2021

Royal College Mock Oral Examiner
2020

Internal Medicine Training Committee
2017- 2018

Patient Oriented Discharge Summary Organizing Committee
2017-2018

Member- Internal Medicine Wellness Committee
2015- 2017

Mentor: Internal Medicine Interest Group
2015-2017

Resident Facilitator: Transition to Residency
2016

Publications

Cowan, A, Gharib, E. and Weir, M. (2017) Advances in the management of hyperkalemia in chronic kidney disease. *Current Opinions in Nephrology and Hypertension.* 26(3): 235-239

Nagpal, D, **Cowan, A**, Li, L., Nusca, G., Novick, R., Harle, C., House, A., Fox, S., and Jones, P. (2020) Starch or Saline After Cardiac Surgery: a Randomized controlled trial. *Canadian Journal of Kidney Health and Disease.* 7: 1-7

Cowan, A and Garg, AX (2020) Controlling pain in dialysis care: a choice among undesirable options. *Nephrology Dialysis Transplantation*. 1-3

Cowan, A, Garg, AX, McArthur, E, Muanda Tsobo, F and Weir, MA. (2020) The cardiovascular safety of metoclopramide compared to domperidone: a population based cohort study. *J Can Ass Gastro*. 4 (5): e110-e119

Cowan, A and House, A. (2021) 'Distinct Cardio Renal Syndromes: Cardiac Surgery Associated Acute Kidney Injury' in McCollough, P. and Ronco, C (ed) *The Textbook of Cardiorenal Medicine*. Springer Books

Gopaul, A, Kanagalingam, T, Thain, J, Khan, T, **Cowan A,** Sultan, N, Clemens, K. (2021) Denosumab in Chronic Kidney Disease: A Narrative Review of Treatment Efficacy and Safety. *Archives of Osteoporosis*

Muanda, F, Weir, M, Ahmadi, F, Sontrop J, **Cowan A,** Fleet J, Blake P, Garg, A (2021) Higher dose gabapentinoids and the risk of adverse events in older adults with CKD: A population-based cohort study. *American Journal of Kidney Disease*

Cowan, A, Jeyakumar, N, Kang, Yunguang, Dixon, S, Garg, Amit, Naylor, K, Weir, M, Clemens, K. (2022) Fracture Risk of Sodium Glucose Cotransporter-2 Inhibitors in Chronic Kidney Disease. *Clinical Journal of the American Society of Nephrology*
* winner of the 2022 CJASN Editor's Choice Award

Bohani,N, Bjazevic, J, Wallace, B, Lee, L, Kaler, K, Dion, M, **Cowan, A,** Sultan, N, Chew, B, Razvi, H. (2022) UPDATE- Canadian Urologic Association guideline: Evaluation and Medical Management of the Kidney Stone Patient. *Canadian Urolology Association Journal*

Cowan, A, Kristin Clemens, Jessica Sontrop, Stephanie Dixon, Lauren Killin, Sierra Anderson,
Rey Acedillo, Amit Bagga, Clara Bohm, Pierre Antoine Brown, Brenden Cote, Varun Dev, Claire Harris, Swapnil Hiremath, Mercedeh Kiaii, Eduardo Lacson Jr, Amber Molnar, Matthew Oliver, Malvinder Parmar, Jennifer M McRae, Bharat Nathoo, Kathleen Quinn, Nikhil Shah, Samuel Silver,
Daniel Tascona, Stephanie Thompson, Robert H Ting, Marcello Tonelli, Hans Vorster, Davinder Wadehra, Ron Wald, Myles Wolf, Amit Garg. (2023). Magnesium and fracture risk in patients across the spectrum of kidney disease: a narrative review. *Canadian Journal of Kidney Health and Disease*

Cowan A, Jeyakumar, N, McArthur E, Fleet, J, Kanagalingam, T, Karp, I, Khan, T, Muanda, F t, Nash, D Silver, A, Thain, J, Weir, Matthew, Garg, A, Clemens, K (2023) Hypocalcemia risk of denosumab across the spectrum of kidney disease: A population-based cohort study. *Journal of Bone and Mineral Research*

Cowan, A, Khan, T, Thain, J, Clemens Kristin K. (2023) Bones of Contention: Predicting and preventing fractures in patients receiving peritoneal dialysis. *Peritoneal Dialysis International*

Presentations

Andrea Cowan, Paul Minda and Mark Goldszmidt. *Basic Science and the Interpretation of the Respiratory Exam: A Needs Assessment.* Poster Presentation. Canadian Conference on Medical Education, Ottawa ON. April 2013

Andrea Cowan, Erin Fleischer and April Price. *Offering Influenza Vaccination at the Point of Clinical Encounter Increases Uptake in the Pediatric Respirology Population.* Poster Presentation. Canadian Respiratory Conference. Halifax, NS. March 2016

Andrea Cowan, Nivethika Jeyakumar, Alexandra M Oedraogo, Amit X Garg, Danielle Nash, Flory Tsobo Muanda, Tayyab Khan, Samuel Silver, Jenny Thain, Matthew A Weir, Igor Karp and Kristin Clemens. *Hypocalcemia Risk of Denosumab in Chronic Kidney Disease: A population Based Study*. Poster Presentation. American Society of Nephrology: Kidney Week. 2021

Andrea Cowan *Fractures in CKD.* Division Grand Rounds, St Michaels Hospital Division of Nephrology 2023 (invited).