

Sex-Based Differences in Cardiovascular Outcomes and Management Approaches in Late-Onset Hypertension

Running Title: Sex Differences in Late-Onset Hypertension

Ann Bugeja, MD FRCPC^{1,2,3}

Thesis Primary Supervisor

Daniel McIsaac, MD MPH FRCPC^{3,4,5}

Thesis Advisory Committee

Claire Kendall, MD PhD CCFP^{3,5,6,7}

Manish Sood MD MSc FRCPC^{2,3}

¹School of Epidemiology and Public Health, University of Ottawa, Ottawa, Ontario

²Division of Nephrology, Department of Medicine, University of Ottawa, Ottawa, Ontario

³Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, Ontario

⁴Departments of Anesthesiology & Pain Medicine, University of Ottawa, Ottawa, Ontario

⁵ICES uOttawa (formerly known as the Institute for Clinical Evaluative Sciences), Ontario

⁶Department of Family Medicine, University of Ottawa, Ottawa, Ontario

⁷Bruyere Research Institute, Ottawa, Ontario

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**School of Epidemiology and Public Health,
Faculty of Medicine, University of Ottawa**

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PREFACE

Author Contributions

The topic for this thesis was developed following discussion with Dr. Ann Bugeja, Dr. Daniel Mclsaac and Dr. Manish Sood.

Dr. Ann Bugeja was involved in and is responsible for every aspect of this thesis: clinical expertise, literature review, ICES privacy training, obtaining health administrative data from ICES, statistical coding and analyses, creation of tables and figures, thesis writing, final proof reading, and thesis submission.

For both manuscripts within this thesis, Dr. Ann Bugeja is the first author and Dr. Daniel Mclsaac is the senior author. Dr. Mclsaac, Dr. Kendall and Dr. Sood assisted in data analysis and critically appraised manuscripts and this thesis, as well as drafting final versions, through discussions and official Thesis Advisory Committee meetings.

Dr. Mclsaac provided supervision and guidance for all aspects of this thesis, including study design and statistical methods. Dr. Sood also provided clinical expertise to help with study design and provided advice on statistical methods.

Ethics review and approval

The data presented in both manuscripts within this thesis originates from de-identified data sourced from ICES uOttawa. ICES, an independent non-profit research institute, is funded by an annual grant from the Ontario Ministry of Health (MOH) and the Ministry of Long-Term Care (MLTC). The use of these data was approved under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a research ethics board. ICES, recognized as a prescribed entity under Ontario's privacy legislation (section 45 of Ontario's Personal Health Information Protection Act, PHIPA), is authorized to collect and use healthcare data for the purposes of health system analysis, evaluation, and decision support. Access to these data is regulated by policies and procedures approved by the Information and Privacy Commissioner of Ontario. Data was accessed through a secure ICES uOttawa server after privacy training with ICES.

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Thesis Abstract

There may be sex-based differences in the care and treatment of people with late-onset hypertension. This thesis aims to investigate the evaluation, initial pharmacological management, and important clinical outcomes, of older adults with a new diagnosis of hypertension. We conducted a population-level cohort study of all Ontario residents 66 years and older with a new diagnosis of hypertension between January 1, 2010 and December 2017. Sex was the exposure. We defined outcomes in the period of 2011 to 2021, with at least 1 year of follow-up. The first manuscript examined a primary outcome that was a composite of adverse cardiovascular events in 266,273 individuals with a new diagnosis of hypertension, defined as: any nonfatal ischemic stroke, nonfatal myocardial infarction, or congestive heart failure, by calculating hazard ratios (HR) using a Cox proportional hazards model. The second manuscript examined 111,410 individuals with a new diagnosis of hypertension but not previously on any medications that could lower blood pressure (BP), in terms of application of Hypertension Canada guideline-recommended investigations for a new diagnosis of hypertension, using Poisson regression. We also examined the initial prescription of a guideline-recommended medication for lowering blood pressure using Cox proportional hazards regression. This thesis shows that females were less likely to have the primary composite outcome despite finding no differences in performance of guideline-recommended investigations for a new diagnosis of hypertension and in prescribing of guideline-recommended medication for hypertension. Unmeasured confounding may account for some of these findings. Our findings suggest that sex-based differences in the outcomes of late-onset hypertension exist, and further studies are required to address these gaps.

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CHAPTER 1: THESIS INTRODUCTION

Ann Bugeja

University of Ottawa

School of Epidemiology and Public Health

Faculty of Medicine

University of Ottawa

CHAPTER 1: OVERVIEW AND OBJECTIVES

Problem

Cardiovascular disease is the leading cause of death for women worldwide, accounting for 35% of deaths in 2019.(1) Hypertension is the strongest, modifiable risk factor for cardiovascular disease and affects at least 23% of women in Canada and 31% (1.3 billion adults) worldwide.(2, 3) Treatment of hypertension can significantly reduce the risk of cardiovascular events and mortality, by 20 and 13%, respectively.(4)

Yet, hypertension disease epidemiology, pathophysiology, treatment and prognosis may differ by sex and gender. Sex-specific differences exist in the pathophysiology of hypertension whereby estrogen modulates most components of the renin-angiotensin-aldosterone system (RAAS) and is associated with lower blood pressure in women. Women also have different physiological responses to medications that block RAAS. (3, 5) Understanding sex-based differences in hypertension-related risk is key for improving women's cardiovascular health and outcomes.(4, 5) Despite its common prevalence in females and well-established biological differences by sex, females are underrepresented in contemporary hypertension trials that are thus unable to systematically explore sex disparities in outcomes.(3, 4, 6)

Complications of hypertension such as stroke and heart failure are sex-dependent, but these associations are largely based on studies in younger populations with prevalent hypertension. Early

studies intermixed new onset (incident) hypertensive patients with existing (prevalent) hypertensive patients, introducing a possible bias in estimates of the association between sex and cardiovascular outcomes.(7-10) While these findings suggest that females may be at higher risk of hypertensive complications, the sex-based differences in mortality limits the validity of these results in the absence of adjusting for death as a competing risk. Furthermore, as a large portion of incident hypertension occurs in older adults (65 years and higher), the generalizability of these findings to the older population is unclear.

New onset hypertension is fourfold higher among postmenopausal females than premenopausal females, whereas the incidence in age-matched males is only threefold, potentially putting older females at greatest risk for cardiovascular morbidity and mortality.(11, 12) Despite this, limited literature exists regarding sex-based differences in outcomes older populations with late onset hypertension. Paradoxically, observational data finds that there is a lower risk of mortality in incident hypertension in older adults compared to younger adults, although data were largely restricted to male participants.(7) Older adults are underrepresented in hypertension studies and in combination with predominant male cohorts, there is a paucity of evidence on the sex-based differences in late-onset hypertension. To further clarify the cardiovascular sequelae of hypertension in women and to encompass the later onset of hypertension in post-menopausal women, hypertension management in older females with new onset hypertension requires examination.

Purpose and Rationale

Older adults who develop hypertension represent an understudied demographic, and critical questions exist regarding their outcomes and processes of care, and whether they differ by sex. Understanding sex-based differences in older adults with incident hypertension could lead to targeted sex-based management of hypertension and help to prevent adverse outcomes. The purpose of this thesis is to examine the care processes and outcomes of late onset hypertension using a population-based retrospective cohort sourced from Ontario's linked health administrative databases.

Objectives

This thesis has three major objectives:

- 1) In older adults with a new diagnosis of hypertension, evaluate sex-based differences in the risk of important cardiovascular outcomes.
- 2) In older adults with a new diagnosis of hypertension, evaluate sex-based differences in the performance of guideline recommended investigations.
- 3) In older adults with a new diagnosis of hypertension, evaluate sex-based differences in the pharmacological treatment based on the guideline-recommended application of first and second antihypertensive medications.

Thesis outline

This is a manuscript-based thesis. Within it, the reader will find two manuscripts presenting the major results for each of the main study questions. The manuscripts are formatted for publication in medical journals. The thesis starts with a background of the literature (Chapter 2) about the differences in the physiology, epidemiology, and management of hypertension by sex and age, and its impact on cardiovascular outcomes. Chapter 3 addresses the first thesis objective, presenting the association between sex and cardiovascular and mortality outcomes in a large population-based cohort of older Ontario adults, in a manuscript titled “Sex-Related Disparities in Cardiovascular Outcomes Among Older Adults With Late-Onset Hypertension” (published in *Hypertension*). Chapter 4 addresses the second thesis objective, examining the management of hypertension by sex in a manuscript titled “Adherence to guideline-recommended care of late onset hypertension in females versus males: A population-based cohort study” (published in the *Journal of Internal Medicine*). The subsequent three chapters are comprised of manuscripts which examine each of our study objectives. Chapter 5 summarizes the findings of the thesis and a discussion about its strengths and limitations and directions for future research.

CHAPTER 2: BACKGROUND

Overview

Cardiovascular disease is the leading cause of death for females worldwide.(13)

Hypertension represents the risk factor with the greatest attributable risk for both all-cause and cardiovascular-related deaths among females, making it the strongest modifiable risk factor for cardiovascular disease. Accordingly, understanding sex-based differences in hypertension-related risk is vital for improving cardiovascular outcomes for females.(4, 5) The recent Lancet Women and Cardiovascular Disease commission has identified hypertension as one of its “most crucial” clinical and research priorities to advance women’s cardiovascular health.(1)

Hypertension affects 24% of Canadians, with attributable healthcare costs estimated to be 13.9 billion CAD in 2010, accounting for 10% of the Canadian healthcare budget.(14, 15) Effective hypertension management reduces cardiovascular events, mitigating factors that worsen quality of life, lead to disability, and increase health care resource utilization.(11) Taken together, these data underscore the importance of screening, detecting, and treating hypertension. Hypertension is confirmed using multiple (preferably automated) office blood pressure readings or out-of-office blood pressure readings. There are variable threshold criteria used internationally for starting antihypertensive therapy but in Canada include: starting at a systolic blood pressure of 130 millimetres of mercury (mmHg) if at high cardiovascular risk or starting at a systolic blood pressure of 130 mmHg or diastolic blood pressure of 80

mmHg if diabetes is present.(16) Choice of pharmacological treatment of hypertension depends on comorbid risk factors, like diabetes, heart failure, coronary artery disease and past stroke. Various treatment targets exist but in Canada, those considered to be at high-risk for cardiovascular disease, including older adults age \geq 75 years, are recommended to have more intensive management to achieve a systolic blood pressure of less than 120 mmHg.(16) Blood pressure targets are the same for females and males but have not been established by randomized controlled trials for older women. Yet, hypertension disease pathophysiology, epidemiology, treatment, and outcomes may differ by sex and gender.

Pathophysiology of hypertension in older adults

Blood pressure rises more precipitously in females than males after middle age. While mechanisms that regulate blood pressure are similar by sex, sex-specific differences exist at the genetic, hormonal, and cellular levels. Genetic predisposition, menopause, obesity, and arterial stiffness are all significant contributors to sex differences in hypertension and cardiovascular outcomes, even though females live longer than males by an average of 5 years. Gene-by-sex interactions exist whereby different polymorphisms contribute to elevated blood pressure in females compared to males. The reduction in estrogen with menopause is associated with endothelial dysfunction (decreased nitric oxide synthesis with consequent increased arterial stiffness, which raises blood pressure), increased body mass index, type 2 diabetes, and sympathetic nervous system activation (increases heart rate and constricts blood

vessels to raise blood pressure), all of which contribute to the development of hypertension.(11) The loss of estrogen in postmenopausal women is also associated with the development of salt sensitivity (i.e. blood pressure increases directly with increased salt intake). However, the exact genetic expressions by age and environmental exposures are not completely understood.(17)

Estrogen modulates most components of the renin-angiotensin-aldosterone system and the endothelin system, and is associated with lower blood pressure in women. In animal models, estrogen inhibits angiotensin II, endothelin 1, and catecholamine synthesis to lower blood pressure. Estrogen also downregulates angiotensin 1 receptor expression in the kidney, adrenal cortex, and vascular smooth muscle cells to lower blood pressure and is lost with age but restored with estrogen replacement.(18) Finally, estrogen promotes sodium excretion by the kidney to lower blood pressure. The impact of estrogen replacement on blood pressure and cardiovascular disease is not well studied, with inconsistent timing between the initiation of hormone replacement relative to menopause onset, lack of placebo group, and differing estrogen dosing regimens in randomized controlled trials.(19, 20)

Weight increases with age and there may also be sex differences in the way obesity modulates the development of hypertension. A comparable increase in body mass index causes a greater rise in systolic blood pressure in females than in males.(11) Leptin, an adipokine that drives hypertension by sympathetic nervous system

activation in males but not in females, stimulates aldosterone synthesis and release in female mice, resulting in hypertension.(21) Subsequently, females with obesity have higher aldosterone levels than males with obesity.(11) Ultimately, females with obesity and hypertension have worse outcomes than males with obesity.

Epidemiology of hypertension in older adults

Sex-specific differences in biology are also reflected in the epidemiology of hypertension. Premenopausal females have a lower prevalence of hypertension compared to both age-matched males and postmenopausal females, regardless of ethnic background. Actual blood pressure then starts to rise from age 60 years onwards among females. The incidence of hypertension is fourfold higher in postmenopausal females than premenopausal women, whereas the incidence in age-matched males increases only threefold. Beyond the age of 75 years, there is a reversal in the sex difference in hypertension prevalence with 81% of females and 73% of males having hypertension, such that older females comprise the majority of the hypertensive population in Canada and the U.S.(5, 11, 22) Consequently, older females may be at greatest risk for increased cardiovascular morbidity and mortality but data supporting or refuting this hypothesis remains inadequate.(5, 7)

Management of hypertension in older adults

Despite the high incidence of late-onset hypertension, there is a paucity of evidence around sex-based differences in its management.(23)(16) (24) Studies suggest that females are both more frequently prescribed medications for blood pressure

management and more often achieve target blood pressure in comparison to males. However, among older adults aged greater than 65 years, older females have more severe hypertension with lower rates of blood pressure control compared to males, despite adjustment for other clinical variables. (25, 26) (3, 6,(27) 8-10) A recent systematic review and meta-analysis highlighted variations in treatment rates, finding a 15% lower prevalent ACE inhibitor use in females compared to males with hypertension and cardiovascular disease.(28) The reasons for sex-related differences in antihypertensive drug use and blood pressure control are unclear. Females are at a higher risk of experiencing adverse effects of antihypertensive medications, which are more severe, compared to males.(29) There may be genetic and physiological factors, inadequate treatment (by health care provider or patient), or inappropriate drug selection that account for differences by sex.(11) Moreover, the evaluation for hypertension following a new diagnosis and *initial* antihypertensive prescription(s) between sexes is also poorly defined particularly in older adults.(10-15) If discrepancies in delivery of guideline-recommended care exist, identifying and addressing care gaps care will lead to improved cardiovascular outcomes.

Outcomes of hypertension in older adults

Treatment of hypertension can significantly reduce the risk of cardiovascular events and mortality, by 20 and 13%, respectively.(4) A meta-analysis of individual patient data for almost one million adults showed that the absolute annual decrease in death from stroke or coronary artery disease attributable to lower systolic blood pressure

increases with age. At age 80-89 years, the absolute benefits of lowering systolic blood pressure are almost ten times greater than at ages 50-59 years.(30) These benefits of lowering blood pressure may be especially relevant for females as recent findings indicate that older females (age ≥ 65 years) from the longitudinal Women's Health Initiative, with few cardiovascular risk factors, have a 73-77% probability of reaching 90 years of age if their systolic blood pressure remains below than 130 mmHg at least 60% of the time.(31) Yet, cardiovascular outcomes by sex among older adults who develop late-onset hypertension (age ≥ 65 years) are not well understood.

Cardiovascular complications of hypertension may also be sex-dependent, but these associations are largely based on studies in younger populations with prevalent hypertension. For example, an observational study of mostly prevalent hypertensive patients ages 40-69 years suggests that the risk of first stroke is higher among females than males after 9 years of follow-up (adjusted hazard ratio 1.36, CI 1.26-1.47)(13). The Framingham study showed that the risk of heart failure among patients with prevalent hypertension is three-fold higher in females compared to two-fold higher in males.(14) A study of 9357 participants from a remote cohort of 11 populations with and without prevalent hypertension, with median 11 years follow-up, found that a 15 mmHg increase in 24-hour systolic blood pressure increased the risk of a cardiovascular event by 56% in females, compared to 32% in males.(15) Additionally, females have a higher risk of myocardial infarction associated with hypertension, compared to males. The INTERHEART study showed that proportion of

myocardial infarctions attributable to hypertension was higher in females than in males (35.8% vs 19.5%) after adjustment for age.(32) However, there is a gap in our knowledge around outcomes among older adults with a new (incident) diagnosis of hypertension. Females with hypertension develop increased arterial stiffness and chronic kidney disease more often than males with increasing age.(1) Previous pregnancy-related conditions, such as gestational hypertension and gestational diabetes, and premature menopause, also contribute to cardiovascular risk.

Differences in outcomes may also be related to gender, and interacting with multiple factors. Taken together, these epidemiologic data suggest that females with higher blood pressure and hypertension may be at higher risk of adverse cardiovascular outcomes but studies focusing on older adults are needed.

Landmark clinical trials in the field have not been designed to specifically assess sex-related differences in outcomes.(16(33-42)) The Systolic Blood Pressure Intervention (SPRINT) trial showed that differences in outcomes were not statistically different between the sexes, but female enrollment was only 36% and event rates were low.(36) The Blood Pressure lowering Treatment Trialists' collaboration compared drug treatment outcomes by sex and found no major differences.(43) However, in a study of older adults, an ACE inhibitor compared with hydrochlorothiazide, prevented myocardial infarction in hypertensive men but not in hypertensive women.(38) Moreover, sex-specific observational studies have not typically evaluated incident hypertension in older adults, leaving an important gap in our understanding of

outcomes in older adults with incident hypertension by sex. Early studies intermixed new onset (incident) hypertensive patients with existing (prevalent) hypertensive patients introducing a possible bias in estimates of the association between sex and cardiovascular outcomes.⁽⁶⁻⁹⁾ Although these findings suggest that females may be at higher risk of hypertensive complications, the observed sex-based differences in mortality limits the validity of these results without adjusting for death as a competing risk. Furthermore, since a large portion of incident hypertension occurs in older adults (age \geq 65 years), the generalizability of these findings to the older population is uncertain. This means that important knowledge gaps exist regarding whether outcomes of hypertension treatment vary by sex in older adults.^(10, 17, 18)

CHAPTER 3: MANUSCRIPT 1:

Sex-Related Disparities in Cardiovascular Outcomes Among Older Adults with Late-Onset Hypertension

Ann Bugeja MD^{1,2,3,4}, Celine Girard MSc^{2,3,5}, Manish M Sood MD MSc^{1,2,3,4}, Claire E Kendall MD PhD^{2,3,5,6}, Ally Sweet⁷, Ria Singla⁷, Pouya Motazedian MD^{2,3,8}, Amanda J Vinson MD, MSc^{9,10}, Marcel Ruzicka, MD PhD^{1,3,4}, Gregory L. Hundemer MD MPH^{1,2,3,4,5}, Greg Knoll^{1,3,4}, Daniel I McIsaac MD MPH^{2,3,5,11}.

Affiliations:

¹Division of Nephrology, Department of Medicine, University of Ottawa and The Ottawa Hospital, Ottawa, Ontario, Canada

²School of Epidemiology & Public Health, University of Ottawa, Ottawa, Ontario, Canada

³Clinical Epidemiology Program, Ottawa Hospital Research Institute, The Ottawa Hospital, Ottawa, Ontario, Canada

⁴Kidney Research Centre, Ottawa Hospital Research Institute, University of Ottawa, Ottawa, Ontario, Canada

⁵ICES uOttawa, Ontario, Canada

⁶Department of Family Medicine, University of Ottawa, Ottawa, Ontario, Canada

⁷Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada

⁸University of Ottawa Heart Institute, Ottawa, Ontario, Canada

⁹Division of Nephrology, Department of Medicine, Dalhousie University

¹⁰Kidney Research Institute Nova Scotia

¹¹Departments of Anesthesiology & Pain Medicine, University of Ottawa and The Ottawa Hospital, Ottawa, Ontario, Canada

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NOVELTY AND RELEVANCE

What is new?

We examined sex differences in important clinical outcomes of older people with late-onset hypertension.

What is Relevant?

25% of older adults in the population developed hypertension.

Females were 25% less likely to experience a composite cardiovascular outcome compared to males.

This finding was consistent after adjusting for the competing risk of all-cause death.

Clinical and Pathophysiological Implications

Future studies should identify potential sex-specific variations in the diagnosis and management of hypertension. This approach will promote targeted and personalized approaches to hypertension management and optimize clinical outcomes in both sexes.

ABSTRACT

Background

It is unclear whether sex-based differences in cardiovascular outcomes exist in late-onset hypertension.

Methods

This is a population-based cohort study in Ontario, Canada of 266,273 adults, age ≥ 66 years with newly diagnosed hypertension. We determined the incidence of the primary composite cardiovascular outcome (myocardial infarction, stroke, and congestive heart failure), all-cause mortality, and cardiovascular death by sex using Cox proportional hazard models adjusted for demographic factors and comorbidities.

Results

The mean age of the total cohort was 74 years, and 135,531 (51%) were female. Over a median follow-up of 6.6 (4.7-9.0) years, females experienced a lower crude incidence rate (per 1000 person years) than males for the primary composite cardiovascular outcome (287.3 versus 311.7), death (238.4 vs 251.4), and cardiovascular death (395.7 vs 439.6), p values < 0.001 . The risk of primary composite cardiovascular outcome was lower among females (adjusted hazard ratio [aHR], 0.75 [95% CI 0.73 to 0.76]; $p < 0.001$) than in males. This was consistent after adjusting for the competing risk of all-cause death with a sub-distributional hazard ratio of 0.88 (95% CI [0.86 to 0.91]; $p < 0.001$).

Conclusions

Females had a lower risk of cardiovascular outcomes compared to males within a population characterized by advanced age and new hypertension. Our results highlight that the severity of outcomes is influenced by sex in relation to the age at which hypertension is diagnosed. Further studies are required to identify sex-specific variations in the diagnosis and management of late-onset hypertension due to its high incidence in this group.

Introduction

Cardiovascular disease is a leading cause of mortality among females worldwide.⁽¹⁾ As hypertension is the most important modifiable risk factor for cardiovascular disease, understanding sex-based differences in hypertension-related risk is key for improving females'

cardiovascular health and outcomes.(2, 3) Despite its common prevalence in females and well-established biological differences by sex, females are underrepresented in contemporary hypertension trials which are thus unable to systematically explore sex disparities in outcomes.(2, 4, 5)

Complications of hypertension such as stroke and heart failure are sex-dependent, but these associations are largely based on studies in younger populations with prevalent hypertension. Early studies intermixed new onset (incident) hypertensive patients with existing (prevalent) hypertensive patients introducing a possible bias in estimates of the association between sex and cardiovascular outcomes.(6-9) While these findings suggest that females may be at higher risk of hypertensive complications, the sex-based differences in mortality limits the validity of these results in the absence of adjusting for death as a competing risk. Furthermore, as a large portion of incident hypertension occurs in older adults (65 years and higher), the generalizability of these findings to the older population is unclear.

New onset hypertension is fourfold higher among postmenopausal females than premenopausal females, whereas the incidence in age-matched males is only threefold, potentially putting older females at greatest risk for cardiovascular morbidity and mortality.(10, 11) Despite this, limited literature exists regarding the outcomes in females of advanced age with late onset hypertension. Paradoxically, observational data finds that there is a lower risk of mortality in incident hypertension in older adults compared to younger adults, although data were largely restricted to male participants.(6) Older adults are underrepresented in hypertension studies and in combination with predominant male cohorts, there is a paucity of evidence on the sex-differences in late-onset hypertension. To further clarify the cardiovascular consequences of hypertension in females and to encompass the later onset of hypertension in post-menopausal females, we examine the cardiovascular outcomes in females of advanced age with new onset hypertension in a contemporary cohort.

Methods

The de-identified, patient-level data used in this study will not be made publicly available.

Study Design and Setting

We conducted a population-based, retrospective cohort study of older adults (66 years and older) who were newly diagnosed with hypertension in Ontario, Canada. This study spanned from January 1, 2010, to December 31, 2021, using linked databases held at the ICES (formerly the Institute for Clinical Evaluative Sciences (ices.on.ca)), which houses the routinely collected healthcare data for over 14 million residents. The utilization of these data was approved in accordance with section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a research ethics board. Our findings are in accordance with the Reporting of studies Conducted using Observational Routinely-collected Data (RECORD) reporting guideline for observational research using routinely gathered data.(12)

Data Sources

We linked several datasets using unique encoded identifiers and analyzed data at ICES. Vital statistics and demographic details were obtained from the Ontario Registered Persons Database. The Canadian Institute for Health Information Discharge Abstract Database provided hospitalizations, diagnoses, and procedural data. Diagnostic data from emergency room and day surgery visits were derived from the National Ambulatory Care Reporting System. We extracted health claims for outpatient and inpatient physician services from the Ontario Health Insurance Plan (OHIP) database. We extracted medication data from the Ontario Drug Benefits database.(13) We used validated codes whenever possible for baseline characteristics and outcomes.(14-20)

Participants

We identified all Ontario residents 66 years and older with incident hypertension between January 1, 2010 and December 31, 2017, using a previously validated case definition with 94% specificity: 1) a hospital admission with an *International Statistical Classification of Diseases and Related Health Problems (ICD-10)*, Tenth Revision code for hypertension or 2) an OHIP claim with a hypertension diagnosis followed within one year by either an additional Ontario Health

Insurance Plan claim or a hospital admission with a hypertension diagnosis.(21) (Table S2 for the full list of ICD-10 codes and OHIP diagnosis codes included.) The index diagnosis date was defined as the second outpatient billing claim for hypertension or hospitalization with hypertension and all patients had at least 1 year of follow-up. We followed patients until a maximum follow-up date of December 31, 2021. Patients were excluded with any of the following: age less than 66 years old, ineligible for OHIP (no valid health card) 1 year prior to index date, non-Ontario resident at index date, death on or before index date.

Exposure

Our exposure was sex assigned at birth (female vs. male) identified from the Registered Persons Database. Self-reported gender is not currently captured in any ICES datasets.

Outcomes

We defined outcomes in the period of 2011 to 2021, with at least one year of follow-up after the index date. The primary cardiovascular composite outcome was a major cardiovascular event defined as: any nonfatal ischemic stroke, nonfatal myocardial infarction, or congestive heart failure.(17-20) Our secondary outcomes were all-cause mortality, coronary revascularization (percutaneous coronary intervention, coronary artery bypass grafting), and cardiovascular death. Cardiovascular death was defined as occurrence of death during a hospitalization or emergency department visit with a cardiovascular diagnosis.(16)

Statistical Analysis

We used descriptive characteristics by exposure status (categorical variables as frequencies and percentages, continuous variables as mean and standard deviation for normally distributed variables, or median and interquartile range for non-normally distributed variables). Differences between exposure levels were quantified using p-values from Kruskal-Wallis tests (with $p < 0.05$ considered significant) and absolute standardized differences, with values >0.1 indicating substantive differences.(22)

We examined the association between sex and time to occurrence of the primary composite cardiovascular outcome using Cox proportional hazards regression, with follow-up beginning from index date. The proportional hazards assumption was assessed and satisfied for the exposure sex, graphically and statistically, using a log-log survival plot.(23, 24) Fine and Gray sub distributional hazard ratios (sHR) were used to account for death as a competing risk for the primary composite cardiovascular outcome and secondary outcome of revascularization and, death and cardiovascular death as a competing risks for revascularization.(25) Models were adjusted for age, era of hypertension diagnosis (2009-2012 or 2012-2017), neighborhood income quintile (as a proxy for socioeconomic status), rural versus urban residence, number of family physician encounters in previous year, number of hospitalizations in previous year, number of total healthcare encounters in previous year, each non-hypertension Elixhauser comorbidity (present or absent, based on a three year lookback).(14, 15) We also adjusted for the use of medications known to lower blood pressure but prescribed for other indications based on our clinical knowledge and previous literature, ascertained in the 120 days closest to cohort entry.(26, 27) Detailed covariates and outcome definitions used in the analyses are outlined in the **Tables S2 and S3**. We tested plausible several effect modifiers of the association between sex and the primary composite cardiovascular outcome a priori and added them to the model individually: age, diabetes, era of hypertension diagnosis (2009-2012 or 2012-2017), a prior cardiovascular diagnosis, and use of blood pressure-lowering medications for other conditions. We tested the p-values for the interaction terms, and as they all demonstrated statistical significance, we present all effect modifiers. We also conducted an additional analysis where we restricted to patients from the top two income quintiles who had visited a family physician in the past year and had no documented comorbidities at baseline, which we thought would reduce confounding due to baseline illness, socioeconomic factors, and health behaviors. Data were missing for income quintile (807, 0.3%) and rural residence (337, 0.1%), but as this represented less than 1% of missing data, analyses proceeded using a complete case design. We report results as hazard ratios (HR) with 95% confidence intervals (CI). Two-sided *P* values <0.05 were considered significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc).

Results

Baseline Characteristics

Among a total of 1,059,026 eligible Ontario residents, 266,273 (25.1%) were ≥ 66 years with incident hypertension. (**Figure 1**) Table 1 shows the baseline characteristics of the complete cohort and by sex. The mean (standard deviation, SD) age was 74 (7) years and 51% of the cohort were female. Females had fewer hypertension diagnoses between 2009-2012, and fewer diagnoses of coronary artery disease, myocardial infarction, diabetes or major cancer within 3 years before their hypertension diagnosis. Among the 154,872 (58.2%) individuals who were already prescribed medication that can lower blood pressure at the time of hypertension diagnosis, females were less likely to be prescribed alpha-blockers, ACE inhibitors, beta blockers, or nitrates. Females were more likely to be prescribed thiazide diuretics. Females were less likely to be prescribed statins. There was no statistically significant difference between sexes in hypertension diagnosed from 2013-2017, or by neighborhood income quintiles, rural residence, other comorbid conditions, or number of blood pressure-lowering medications at baseline.

Outcomes

The median (IQR) follow-up was 6.6 (4.7-9.0) years with no statistically significant difference between the sexes (p value = 0.4). For the primary composite cardiovascular outcome of nonfatal stroke, myocardial infarction, or congestive heart failure, there were 38,586 events in the cohort, of which 17,642 (45.7%) were among females. Compared to males, females had a lower crude incidence rate (per 1000 person years) of the primary composite cardiovascular outcome (287.3 in females versus 311.7 in males, $p < 0.001$). Females had a significantly lower risk of the primary composite cardiovascular outcome than males (unadjusted hazard ratio [HR] 0.76, [95% CI 0.75, 0.78]; adjusted hazard ratio [aHR] 0.75, [95% CI 0.73, 0.76]). (**Figure 2**) The subdistributional hazard ratio (sHR) for the primary outcome accounting for the competing risk of all-cause death was 0.88 for females compared to males, (95% CI 0.86, 0.91). (**Table 2, Table S4**)

There were a total of 77,005 deaths, with 35,189 (45.7%) occurring in females. Compared to males, females had a lower crude incidence rate of all-cause death compared to males (238.4 per 1000 person years in females versus 251.4 in males, $p < 0.001$) and lower unadjusted and adjusted hazard of all-cause death compared to males (HR 0.77 95% CI [0.76, 0.78], aHR 0.72, 95% CI [0.71, 0.73], respectively). Among the 9,234 participants with cardiovascular deaths, 4,020 (43.5%) deaths occurred in females. Compared to males, females had a lower crude incidence rate of cardiovascular related death compared to males (395.7 per 1000 person years in females versus 439.6 in males, p value < 0.001), and a lower hazard for cardiovascular death than males (HR 0.88 [0.84, 0.92], aHR 0.85, 95% CI [0.82, 0.99]). There were a total of 24,031 revascularization events, with 6,976 (29.0%) in females. Compared to males, females had a lower crude incidence rate of revascularization compared to males (398.8 per 1000 person years in females versus 482.3 in males, p value < 0.001). Females had a lower hazard for undergoing a revascularization procedure (HR 0.86, 95% CI [0.84, 0.89], aHR 0.91, 95% CI [0.89, 0.94]), even after accounting for all-cause death (sHR 0.47, 95% CI [0.46, 0.49]) and cardiovascular death (sHR 0.45 95% CI [0.43, 0.46]). (Table 2)

Stratified Analyses

Older age, diabetes, a previous cardiovascular diagnosis, earlier hypertension diagnosis, and pre-existing use of blood pressure-lowering medication were statistically significant effect modifiers of the primary composite cardiovascular outcome ($p \leq 0.01$). (**Figure S1**) In stratified analyses comparing females to males, females had a lower hazard of the primary composite cardiovascular outcome regardless of whether they had a previous cardiovascular diagnosis (aHR 0.91, 95% CI [0.83, 0.99] vs aHR 0.75, 95% CI [0.73, 0.77]), or diabetes (aHR 0.82, 95% CI [0.79, 0.86] vs aHR 0.73, 95% CI [0.72, 0.75]), or a more recent vs remote diagnosis of hypertension (aHR 0.74, 95% CI [0.71, 0.76] vs aHR 0.77, 95% CI [0.74, 0.79]), or when prescribed one or more blood pressure-lowering medications or not (aHR 0.77, 95% CI [0.75, 0.78] vs aHR 0.68, 95% CI [0.64, 0.73]).

Additional Analysis

An additional analysis conducted on a subgroup of 3,635 individuals from the top two income quintiles who had visited a family physician was consistent in demonstrating an association between female sex and lower risk of the primary composite cardiovascular outcome (HR 0.72 95% CI [0.59, 0.88]).

Discussion

Principal findings

In this population-based study of newly diagnosed hypertension in older adults, females had a lower risk of cardiovascular events than males. This was consistent for our primary composite cardiovascular outcome (stroke, myocardial infarction, heart failure), cardiovascular death, revascularization, and all-cause death in crude and adjusted analyses accounting for the competing risk of death, as well as across all postulated effect modifiers (previous cardiovascular disease, diabetes, era of hypertension diagnosis, use of blood pressure lowering medication).

Our findings suggest that older females with newly diagnosed hypertension are not at higher risk of cardiovascular outcomes and death compared to older males, despite existing estimates from non-risk adjusted cohorts and studies of younger adults suggesting otherwise.(9, 10, 28, 29) This illustrates the importance of consideration of incident hypertension in older adults.

Comparison with other studies

Current evidence on sex-specific outcomes for incident hypertension in older populations is limited and, as a result, evidence from younger cohorts is extrapolated.(9, 10) In contrast to our findings, previous studies have documented higher complication rates in hypertensive females compared to males; however these findings are typically derived from younger cohorts. In a large observational study, females (age 40-69 years) with hypertension had a 36% higher risk of stroke compared to males.(30) The Framingham study reported a higher risk of incident heart failure in females compared to males.(8) The International Database of Ambulatory blood pressure in relation to Cardiovascular Outcome (IDACO) study found that a 15 mmHg increase

in systolic blood pressure was more strongly associated with adverse cardiovascular events in females compared to males but with much lower crude incidence rates of 11-12 per 1000 person years for death and cardiovascular outcomes than found in our study.(9) Statistical inference from these studies is limited, as the prevalence of hypertension complications is higher in females due to their longer life expectancy and these studies do not adjust for the competing risk of death.(31) Indeed, a registry cohort of younger patients with *incident* hypertension (median age 56 years for females and 53 years for males), demonstrated that males were on more blood pressure-lowering medications, which could indicate that they have more difficult-to-control hypertension. Additionally, males in our study were more likely than females to have diabetes at the time of hypertension diagnosis, which is an indication for prescribing ACE inhibitors. However, our model accounted for the number of blood pressure lowering medications and findings persisted in stratified analyses by both pre-existing diabetes and pre-existing presence of blood pressure-lowering medication. Ultimately, prospective studies of sex-based outcome differences after incident hypertension diagnosis and population-based studies of sex-specific treatment processes and outcomes are required to untangle these complex causal pathways.

Strengths and Limitations

While our findings are strengthened by our large cohort size and consistency across stratified analyses, it also has limitations. First, we lacked specific information on blood pressure measurement data. While our findings consistently demonstrated lower risk of cardiovascular outcomes and death for females in all analyses, we are unable to comment on difference in outcomes based on the degree of hypertension treatment between the sexes. Second, our findings are limited to sex-based findings and cannot be extrapolated to gender, although there is a strong literature base on the influence of gender as a social construct for hypertension outcomes.(10, 32-35, 37) We also lacked the racial and ethnic composition of our cohort. Third, we were unable to include some key variables related to menopausal and reproductive history, such as gestational hypertension and pre-eclampsia, that predisposes females to hypertension. Fourth, body mass index measurements, cholesterol data, and smoking status were unavailable

in our datasets. As smoking is a risk factor for cardiovascular outcomes and death, and is more common among males, this would serve as a potential confounder.⁽³⁸⁾ Lastly, our study is limited to a single health care system.

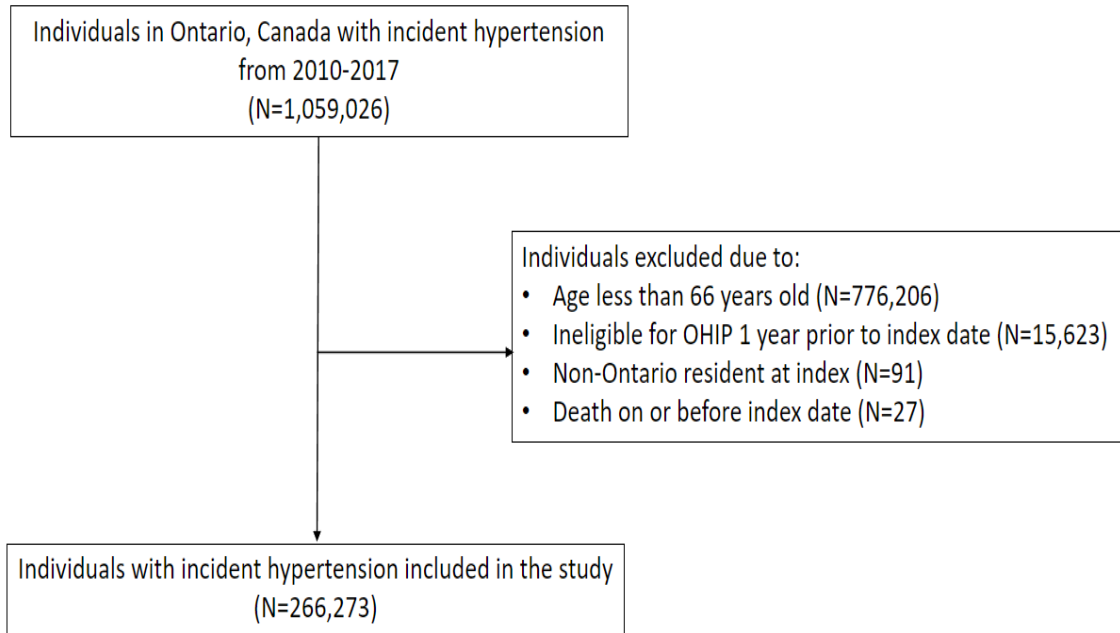
In our population-level, observational study of 266,273 people with late-onset hypertension, we found that there are sex-specific differences in cardiovascular outcomes and death. Importantly, and contrary to what has been observed amongst younger cohorts where females with hypertension are higher risk for cardiovascular events, female sex was protective against adverse cardiac outcome amongst older patients with hypertension in our current study. Given the high incidence of hypertension in this patient cohort, future studies should identify potential sex-specific variations in the diagnosis and management of hypertension. This approach will promote targeted and personalized approaches to hypertension management and optimize clinical outcomes.

Conclusions

This study shows that older females with newly diagnosed hypertension have a lower risk of cardiovascular outcomes and death compared to older males. This may be related to underlying biology, awareness and hypertension management, and psychosocial factors. Given the high incidence of hypertension observed in this study, these findings are particularly important in the context of a growing older population. Future studies should identify potential sex-specific variations in the diagnosis and management of hypertension. This approach will promote targeted and personalized approaches to hypertension management and optimize clinical outcomes in both sexes.

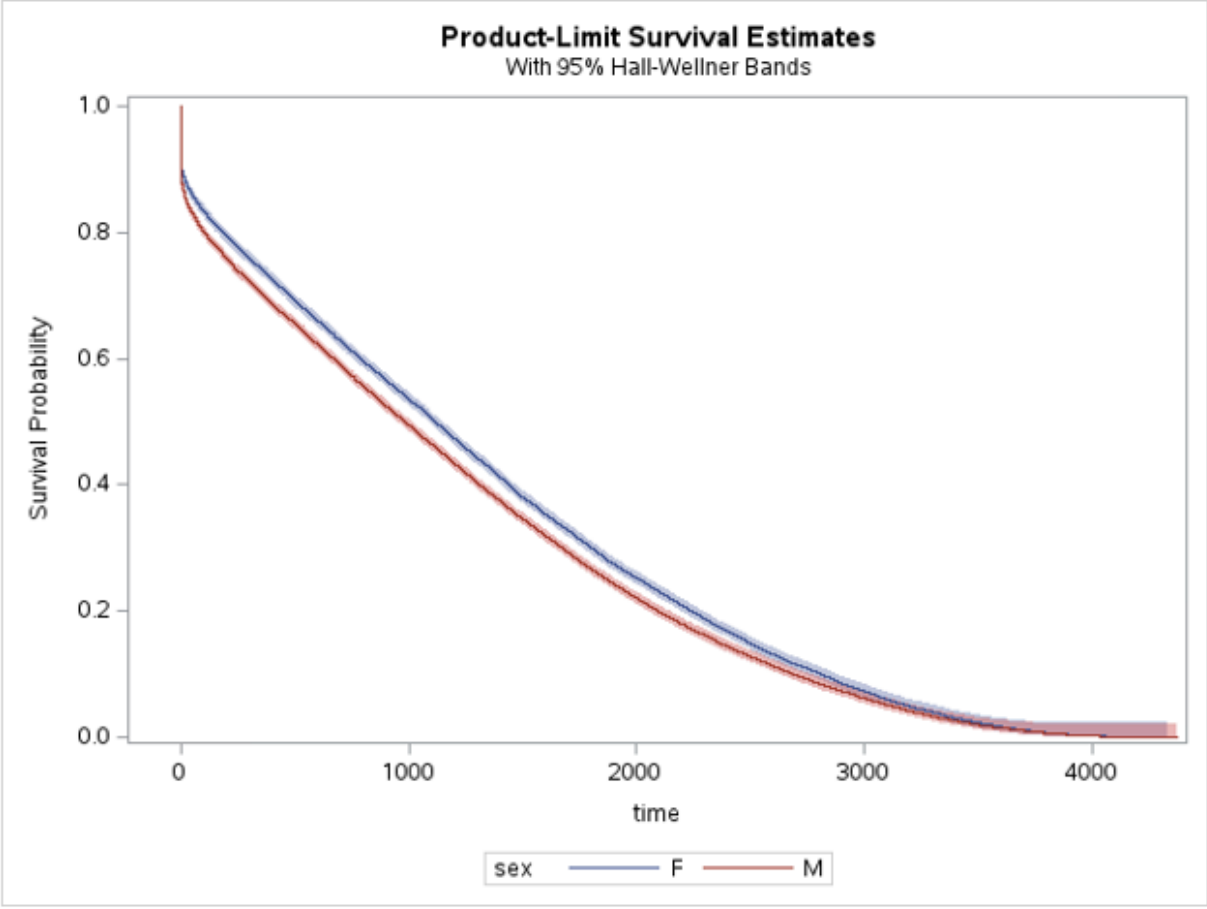
FIGURES (Chapter 3)

Figure 1. Flow Diagram for Cohort Assembly



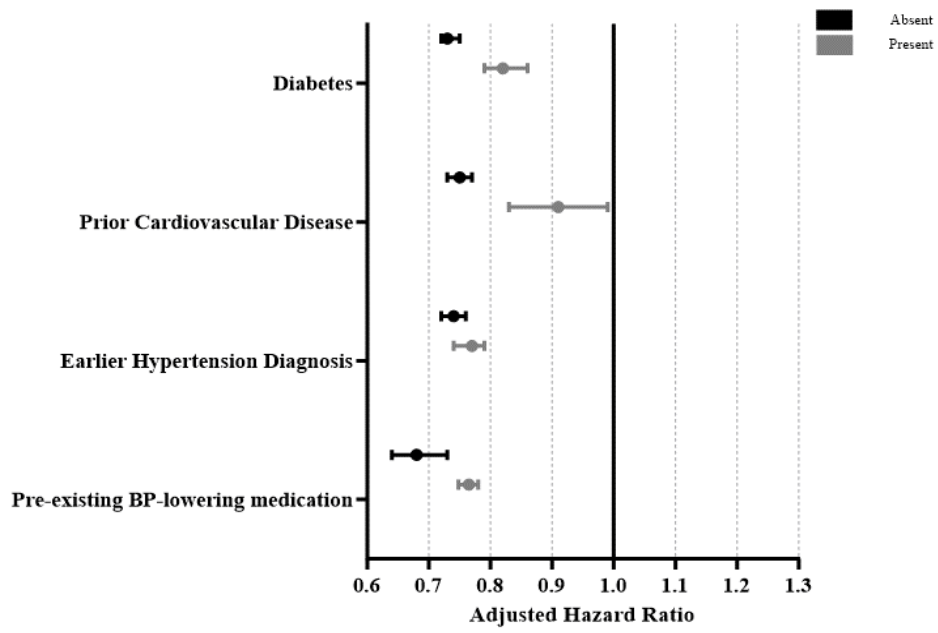
OHIP refers to Ontario Health Insurance Plan

Figure 2. Kaplan-Meier plots for the primary cardiovascular outcome (survival probability) with newly diagnosed hypertension by sex over time



Supplemental Figure S1. Effect modifiers of the primary composite cardiovascular outcome. Prior cardiovascular disease was defined as the presence of myocardial infarction, ischemic stroke, or congestive heart failure at baseline. Pre-existing BP-lowering medication refers to the use of any medication that lowers blood pressure at baseline. Error bars represent 95% CIs.

| | Number at risk | Number with MACE event | Adjusted Hazard Ratio (95% CI) | p value for interaction with sex |
|---|----------------|------------------------|--------------------------------|----------------------------------|
| Total | 266,273 | 38,586 | | |
| Age | | | 1.07 (1.07, 1.07) | |
| Diabetes | | | | <0.01 |
| Absent | 213,450 | 29,147 | | |
| Female | 100,222 | 13,956 | 0.73 (0.72, 0.75) | |
| Male | 113,228 | 15,191 | ref | |
| Present | 52,823 | 9,439 | | |
| Female | 22,303 | 3,686 | 0.82 (0.79, 0.86) | |
| Male | 30,520 | 5,753 | ref | |
| Prior CV diagnosis | | | | <0.01 |
| Absent | 253,252 | 36,237 | | |
| Female | 130,542 | 16,788 | 0.75 (0.73, 0.77) | |
| Male | 122,710 | 19,449 | ref | |
| Present | 13,021 | 2,349 | | |
| Female | 4,989 | 854 | 0.91 (0.83, 0.99) | |
| Male | 8,032 | 1,495 | ref | |
| Diagnosis of Hypertension | | | | 0.01 |
| 2009-2012 | 101,347 | 18,903 | | |
| Female | 52,266 | 8907 | 0.77 (0.75, 0.79) | |
| Male | 49,081 | 9,996 | ref | |
| 2013-2017 | 164,926 | 19,683 | | |
| Female | 83,265 | 8,735 | 0.74 (0.72, 0.76) | |
| Male | 81,661 | 10,948 | ref | |
| Pre-existing lower BP medication | | | | <0.01 |
| Absent | 111,410 | 14,003 | | |
| Female | 59,422 | 6,582 | 0.68 (0.64, 0.73) | |
| Male | 51,988 | 7,421 | ref | |
| Present | 154,863 | 24,583 | | |
| Female | 76,109 | 11,060 | 0.77 (0.75, 0.78) | |
| Male | 78,754 | 13,523 | ref | |



TABLES (Chapter 3)

Table 1. Baseline characteristics among individuals with a new diagnosis of hypertension by sex

| Characteristic | Complete cohort N=266,273 | Female N=135,531 | Male N=130,742 | St. diff |
|--|--------------------------------------|-----------------------------|---------------------------|-----------------|
| Age, y, mean (SD) | 74 (7) | 74 (7) | 74 (6) | 0.02 |
| Follow-up duration in years, median (IQR) | 6.6 (4.7-9.0) | 6.8 (4.8-9.2) | 6.5 (4.5-8.8) | |
| Income Quintile* | | | | p<0.001 |
| Quintile 1: lowest | 51298 | 27176 (20.1) | 24122 (18.4) | |
| Quintile 2 | 54547 | 28397 (21.0) | 26150 (20.0) | |
| Quintile 3 | 53325 | 27030 (19.9) | 26295 (20.1) | |
| Quintile 4 | 52519 | 26125 (19.3) | 26394 (20.2) | |
| Quintile 5: highest | 54584 | 26803 (19.8) | 27781 (21.2) | |
| Era of hypertension diagnosis | | | | p<0.001 |
| 2009-2012 | 101347 | 52266 (51.6) | 49081 (61.1) | |
| 2013-2017 | 164926 | 83265 (61.4) | 81661 (62.6) | |
| Rural residence | 32697 | 15086 (13.5) | 17611 (11.1) | |
| Comorbid conditions | | | | |
| Coronary artery disease | 28972 | 9731 (7.2) | 19241 (14.7) | 0.24 |
| Myocardial infarction | 6033 | 1929 (1.4) | 4104 (3.1) | 0.12 |
| CABG | 1446 | 406 (0.3) | 1040 (0.8) | 0.07 |
| Congestive heart failure | 5587 | 2369 (1.8) | 3218 (2.5) | 0.05 |
| Atrial fibrillation | 7177 | 3132 (2.3) | 4045 (3.1) | 0.05 |
| Arrhythmia | 10625 | 4563 (3.4) | 6062 (4.6) | 0.06 |
| Ischemic stroke | 2699 | 1149 (0.8) | 1550 (1.2) | 0.03 |
| Peripheral vascular disease | 2152 | 628 (0.5) | 1524 (1.2) | 0.08 |
| Diabetes | 52823 | 22303 (16.5) | 30520 (23.3) | 0.17 |
| COPD | 7658 | 3719 (2.7) | 3939 (3.0) | 0.02 |
| Chronic liver disease | 4115 | 1753 (1.3) | 2362 (1.8) | 0.04 |
| Major cancer | 24275 | 9109 (6.7) | 15166 (11.6) | 0.17 |
| Seizure | 788 | 340 (0.2) | 448 (0.3) | 0.02 |
| Osteoporosis | 770 | 648 (0.5) | 122 (0.09) | 0.07 |
| Chronic renal disease | 1849 | 625 (0.5) | 1224 (0.9) | 0.06 |
| Dementia | 3917 | 2118 (1.6) | 1799 (1.4) | 0 |
| No. of BP-lowering medications | | | | p<0.001 |
| 0 | 111401 | 59414 (43.8) | 51987 (39.8) | |
| 1 | 97815 | 50884 (37.5) | 46931 (35.9) | |
| 2 | 38729 | 17518 (12.9) | 21211 (16.2) | |
| 3 | 13948 | 5925 (4.4) | 8023 (6.1) | |
| 4 | 3679 | 1515 (1.1) | 2164 (1.7) | |

| | | | | |
|---------------------------------------|---------|------------------|---------------|------|
| 5+ | 701 | 275 (0.2) | 426 (0.3) | |
| Medications | | | | |
| Alpha blocker | 3431 | 187 (0.1) | 3244 (2.5) | 0.21 |
| ACE inhibitor | 69459 | 30062 (22.2) | 39397 (30.1) | 0.18 |
| ARB | 33417 | 17709 (13.1) | 15708 (12.0) | 0.03 |
| Beta blocker | 44696 | 19312 (14.3) | 25384 (19.4) | 0.14 |
| Calcium channel blocker | 36085 | 18765 (13.9) | 17320 (13.3) | 0.02 |
| Hydralazine | 222 | 88 (0.1) | 134 (0.1) | 0.01 |
| Thiazide diuretic | 21959 | 13369 (9.9) | 8590 (6.6) | 0.12 |
| Loop diuretic | 14927 | 7311 (5.4) | 7616 (5.8) | 0.02 |
| Nitrate | 10919 | 4110 (3.0) | 6809 (5.2) | 0.11 |
| Clonidine | 309 | 244 (0.2) | 65 (0.1) | 0.04 |
| Antiarrhythmic | 1533 | 609 (0.4) | 924 (0.7) | 0.03 |
| SGLT-2 inhibitor | 770 | 275 (0.2) | 495 (0.4) | 0.03 |
| Statin | 105,304 | 46,294 (34.2) | 59,010 (45.1) | 0.22 |
| Health Services | | | | |
| Family physician visits (median, IQR) | 6(7) | 6(7) | 6(7) | |
| ED visits (median, IQR) | 0(1) | 0(1) | 0(1) | |
| Hospitalizations (median, IQR) | 0(1) | 0(1) | 0(1) | |

Values are number (percentage), unless specified as mean (standard deviation (SD)) or median (interquartile range). p-values are reported for Kruskal-Wallis tests.

*Income quintile missing in 807, 0.3% of cohort

¥ Rural residence, defined as residing in a location with population <10000, missing in 337, 0.1% of cohort

Table 2. Events, crude incidence rates, unadjusted HRs, adjusted HRs, and Fine and Gray sHRs by sex

| OUTCOME | Event frequency (N, %) | Crude incidence rate per 1000 | HR (95% CI) | aHR* (95% CI) | sHR* (95% CI) for death | sHR* (95% CI) for CV death |
|---|-------------------------------|--------------------------------------|--------------------|----------------------|--------------------------------|-----------------------------------|
| Primary composite CV outcome (MI/stroke/CHF) | 38,586/266,273 (15.0) | 300.0 | 0.76 (0.75, 0.78) | | | |
| Male | 20,944/130,742 (16.0) | 311.7 | | | 1.00 (ref) | |
| Female | 17,642/135,531 (13.0) | 287.3 | | 0.75 (0.73, 0.76) | 0.88 (0.86, 0.91) | |
| Death | 77,005/266,273 (28.9) | 245.3 | 0.77 (0.76, 0.78) | | | |
| Male | 41,816/130,742 (32.0) | 251.4 | | | 1.00 (ref) | |
| Female | 35,189/135,531 (30.0) | 238.4 | | 0.72 (0.71, 0.73) | | |
| CV death | 9,234/266,273 (3.5) | 419.3 | 0.88 (0.84, 0.92) | | | |
| Male | 5,214/130,742 (4.0) | 439.6 | | | 1.00 (ref) | |
| Female | 4,020/135,531 (3.0) | 395.7 | | 0.85 (0.82, 0.99) | | |

| | | | | | | |
|--------------------------|-----------------------|-------|-------------------|-------------------|-------------------|-------------------|
| | | | | | | |
| Revascularization | 24,031/266,273 (9.0) | 454.7 | 0.86 (0.84, 0.89) | | | |
| Male | 17,055/130,742 (13.0) | 482.3 | | 1.00 (reference) | | |
| Female | 6,976/135,531 (5.2) | 398.8 | | 0.91 (0.89, 0.94) | 0.47 (0.46, 0.49) | 0.45 (0.43, 0.46) |

*HRs were adjusted for age, income quintile, rural vs urban residence, era of hypertension diagnosis, past cardiovascular disease, chronic obstructive pulmonary disease, chronic kidney disease, ischemic stroke, peripheral vascular disease, diabetes, cancer, osteoporosis, seizure disorder, chronic liver disease, dementia; use of any BP-lowering medication and type of BP-lowering medication in past 120 days; emergency department visit, family doctor visit, hospitalization in the previous year.

aHR, adjusted hazard ratio, sHR, subdistributional hazard ratio, CV, cardiovascular

CHAPTER 4: MANUSCRIPT 2: Adherence to guideline-recommended care of late-onset hypertension in females versus males: A population-based cohort study

Ann Bugeja MD^{1,2,3,4}, Celine Girard MSc^{2,3,5}, Manish M Sood MD MSc^{1,2,3,4}, Claire E Kendall MD PhD^{2,3,5,6}, Ally Sweet⁷, Ria Singla⁷, Pouya Motazedian MD^{2,3,8}, Amanda J Vinson MD, MSc^{9,10}, Marcel Ruzicka, MD PhD^{1,3,4}, Gregory L. Hundemer MD MPH^{1,2,3,4,5}, Greg Knoll^{1,3,4}, Daniel I McIsaac MD MPH^{2,3,5,11}.

Affiliations:

¹Division of Nephrology, Department of Medicine, University of Ottawa and The Ottawa Hospital, Ottawa, Ontario, Canada

²School of Epidemiology & Public Health, University of Ottawa, Ottawa, Ontario, Canada

³Clinical Epidemiology Program, Ottawa Hospital Research Institute, The Ottawa Hospital, Ottawa, Ontario, Canada

⁴Kidney Research Centre, Ottawa Hospital Research Institute, University of Ottawa, Ottawa, Ontario, Canada

⁵ICES uOttawa, Ontario, Canada

⁶Department of Family Medicine, University of Ottawa, Ottawa, Ontario, Canada

⁷Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada

⁸University of Ottawa Heart Institute, Ottawa, Ontario, Canada

⁹Division of Nephrology, Department of Medicine, Dalhousie University

¹⁰Kidney Research Institute Nova Scotia

¹¹Departments of Anesthesiology & Pain Medicine, University of Ottawa and The Ottawa Hospital, Ottawa, Ontario, Canada

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Abstract

Importance: Sex-based disparities in cardiovascular outcomes may be improved with appropriate hypertension management.

Objective: To compare evidence-based evaluation and management of females with late onset hypertension compared to males in the contemporary era.

Design: Retrospective population-based cohort study.

Setting: Ontario, Canada.

Participants: Residents age ≥ 66 years with newly diagnosed hypertension between January 1, 2010, and December 31, 2017.

Exposure: Sex (female vs male)

Main Outcomes and Measures: We used Poisson and logistic regression to estimate adjusted sex-attributable differences in the performance of guideline-recommended lab investigations. We estimated adjusted differences in time to the prescription of, and type of, first antihypertensive medication prescribed between females and males, using Cox regression.

Results: Among 111,410 adults (mean age 73 years, 53% female, median follow-up 6.8 years), females underwent a similar number of guideline-recommended investigations (adjusted incidence rate ratio, 0.997 [95% CI 0.99 to 1.002]) compared to males. Females were also as likely to complete all investigations (0.70% females, 0.77% males; adjusted odds ratio, 0.96 [95% CI 0.83 to 1.11]). Females were slightly less likely to be prescribed medication (adjusted hazard ratio [aHR] 0.98 [95% CI 0.96 to 0.99]) or among those prescribed, less likely to be prescribed first-line medication (aHR, 0.995 [95% CI 0.994 to 0.997]).

Conclusions and Relevance: Compared to males, females with late-onset hypertension were equally likely to complete initial investigations with comparable prescription rates. These findings suggest that there may be no clinically meaningful sex-based differences in the initial management of late-onset hypertension to explain sex-based disparities in cardiovascular outcomes.

Introduction

A call to action has been issued for a better understanding of sex-based differences in hypertension, as sex-specific care is a fundamental component in advancing women's cardiovascular health and mortality.(1, 2) Females exhibit distinct patterns of blood pressure regulation and hormonal influences.(3, 4) While genetic and physiological differences exist, there are also treatment differences highlighted by a recent systematic review and meta-analysis finding a 15% lower prevalent ACE inhibitor use in females compared to males with hypertension and cardiovascular disease.(5) Understanding where sex-based differences do and do not exist can inform sex-specific considerations into guidelines, improving treatment effectiveness and burden of cardiovascular disease.(6, 7)

Blood pressure management and control may vary by sex. Women may be more likely to be adherent to medication and achieve target blood pressure, but this has not been demonstrated consistently.(8, 9) Differences in the hypertension management have been described, but the evaluation and antihypertensive prescription at the time of diagnosis between sexes has been poorly defined.(10-15) This includes the use of ancillary investigations following a new diagnosis and appropriate prescribing of *guideline-recommended* first-line antihypertensive medication at the time of diagnosis. If discrepancies in delivery of guideline-recommended care exist, identifying and addressing care gaps care will lead to improved cardiovascular outcomes. Furthermore, with incident hypertension being common but understudied in older populations, there is a paucity of evidence around sex-based differences in the management of late-onset hypertension.(16) Therefore, the objective of our study is to examine the management of newly

diagnosed hypertension in older females compared to older males within a contemporary cohort.

Methods

Study Design and Setting

We conducted a population-based, retrospective cohort study of older adults (≥ 66 years of age) with newly diagnosed hypertension (incident cohort) in Ontario, Canada. This study, covering the period from January 1, 2010, to December 31, 2021, utilized linked databases held at the ICES (formerly the Institute for Clinical Evaluative Sciences (ices.on.ca)), which holds healthcare data routinely collected for over 14 million residents. Data use was authorized under section 45 of Ontario's Personal Health Information Protection Act and does not require a research ethics board review. We report the study using the RECORD guideline for observational research.(Supplemental Table S1)

Data Sources

We linked several datasets using unique encoded identifiers and analyzed data at ICES. Vital statistics and demographic details were obtained from the Ontario Registered Persons Database. The Canadian Institute for Health Information Discharge Abstract Database provided diagnoses. Diagnostic data from emergency room and day surgery visits were derived from the National Ambulatory Care Reporting System. We extracted health claims for outpatient and inpatient physician services from the Ontario Health Insurance Plan (OHIP) database. In Ontario, medications are captured for individuals 65 years and older. We included individuals at age 66 years and above to allow for a 1-year lookback for baseline medication usage. We extracted medication data from the Ontario Drug Benefits database.(17) Laboratory information for Ontario residents is contained in the Ontario Laboratories Information System. We used validated codes whenever possible for cohort creation, baseline characteristics, and outcomes.(18-24)

Population

We identified all Ontario residents ≥ 66 years with a new diagnosis of hypertension between January 1, 2010 and December 31, 2017, using a previously validated case definition with 94% specificity: 1) a hospital admission with an *International Statistical Classification of Diseases and Related Health Problems (ICD-10)*, Tenth Revision code for hypertension or 2) an OHIP claim with a hypertension diagnosis followed within one year by either an additional OHIP claim or a hospital admission with a hypertension diagnosis.⁽²⁵⁾ (Supplementary Table S2 for the full list of ICD-10 codes and OHIP diagnosis codes included.) The index diagnosis date was defined as the second outpatient billing claim for hypertension or hospitalization with hypertension and all patients had at least one year of follow-up. We followed patients until a maximum follow-up date of December 31, 2021. Patients were excluded with any of the following: age less than 66 years old, no valid health card, 1 year prior to index date, non-Ontario resident at index date, death on or before index date, prescription of a medication known to lower blood pressure within one year prior to the index date.

Exposure

Our exposure was biologic sex (female vs. male) identified from the Registered Persons Database. Self-reported gender is not currently captured in ICES datasets.

Outcomes

We defined outcomes in the period of 2011 to 2021. We selected outcomes aligning with standard of care processes related to the evaluation and management of newly diagnosed hypertension. The 2010 Hypertension Canada guidelines was used to assess standard of care as it remained consistent over the full study period.⁽²⁶⁾ The first process was a count of guideline-recommended investigations for a new diagnosis of hypertension: sodium, potassium, creatinine, lipid profile, fasting blood glucose or hemoglobin A1c, urinalysis, and a 12-lead electrocardiogram.⁽²⁶⁾ As an alternative outcome measure, we also created a binary outcome based on completion of guideline-recommended investigations for hypertension, defined as

having completed all seven recommended investigations. We further examined the first medication(s) prescribed for the diagnosis of hypertension, including whether the prescribed agent was guideline-recommended. To define guideline-recommended treatment, the 2010 Hypertension Canada guidelines require consideration of an individual's comorbidities, including diabetes, stroke, congestive heart failure (CHF), myocardial infarction, coronary artery disease (CAD) and chronic kidney disease. (Supplemental Material Table S4 for list of definitions of a recommended antihypertensive therapy).(27)

Statistical Analysis

We describe characteristics by exposure status (categorical variables as frequencies and percentages, continuous variables as mean and standard deviation for normally distributed variables, or median and interquartile range for non-normally distributed variables). Differences between exposure levels were quantified using absolute standardized differences, with values >0.1 indicating substantive differences.(28). Two-sided P values <0.05 were considered significant.

We conducted unadjusted and adjusted Poisson regression analyses to estimate the association between sex and performance of guideline-recommended investigations, using the count of investigations performed within one year (before and after) index date, as the dependent variable. We used logistic regression to estimate the association of sex with completion of investigations. To estimate the association of sex with time to prescription of guideline-recommended treatment, we used Cox proportional hazards regression, with follow-up beginning from the index date. The proportional hazards assumption was satisfied for the exposure variable, graphically and statistically, using a cumulative incidence function plot.(29)

We adjusted all analyses for age, era of hypertension diagnosis (2010-2012 or 2012-2017), neighborhood income quintile (proxy for socioeconomic status), rural versus urban residence, number of family physician encounters in previous year, number of hospitalizations in previous year, number of total healthcare encounters in previous year, each non-hypertension Elixhauser comorbidity (present/absent, based on a three-year lookback).(18, 19) Detailed covariates and outcome definitions used in the analyses are outlined in the Supplemental

Material Tables S2 and S3. We report results as incidence rate ratios (IRR), odds ratios (OR), or hazard ratios (HR) with 95% confidence intervals (CI).

We also examined the association between sex and prescription of recommended antihypertensive treatment in 4 pre-specified subgroups: diabetes, stroke, CAD, and CHF. We tested plausible effect modifiers of the association between sex and prescription of a recommended antihypertensive treatment a-priori, by adding a multiplicative interaction term between sex and the effect modifier to the model individually: age, diabetes, era of hypertension diagnosis (2010-2012 or 2012-2017), and prior cardiovascular disease. We estimated p-values for the interaction terms, and present those that reached statistical significance. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary NC).

Results

Baseline Characteristics

Among a total of 1,059,026 Ontario residents with incident hypertension during the study period, 111,410 (10.5%) were aged 66 years and above with incident hypertension and without prior prescriptions for antihypertensive medications. (Figure 1) Among them, there were 59,422 (53.3%) females and 51,988 (46.7%) males. Table 1 shows the baseline characteristics of the complete cohort and by sex. The mean (standard deviation, SD) age was 73 (SD 7) years. Females had fewer diagnoses of diabetes, CAD or major cancer within 3 years before their hypertension diagnosis. There was no significant difference between sexes in hypertension diagnosed from 2013-2017, or by neighborhood income quintiles, rural residence, or other comorbid conditions at baseline. There were no missing data. The median (IQR) follow-up was 6.8 (4.8-9.2) years with no significant difference between the sexes (p value = 0.5).

Outcomes

Investigations performed for a new diagnosis of hypertension

57,504 (96.8%) females and 51,988 (96.7%) males had at least one investigation performed. (Table 2) The mean (SD) number of investigations performed was 4.5 (SD 1.8) in both sexes. Compared to males, females had a lower unadjusted rate of guideline-recommended testing for newly diagnosed hypertension (unadjusted IRR 0.99, [95% CI 0.98, 0.99]), but the adjusted results were not different (adjusted IRR 0.997, [95% CI 0.99, 1.002]). Only 414 (0.70%) females and 399 (0.77%) males completed all seven guideline-recommended investigations. Urinalysis was the least performed test, conducted for only 1,573 (1.4%) individuals. There was no difference in having completed all seven guideline-recommended investigations for newly diagnosed hypertension by sex (unadjusted odds ratio 0.91, [95% CI 0.79, 1.04]; adjusted odds ratio 0.96, [95% CI 0.83, 1.11]).

Older age of diagnosis and period effect of hypertension diagnosis were effect modifiers of receiving guideline-recommended investigations for newly diagnosed hypertension. Females were less likely to undergo testing with increasing age. In stratified analyses, females were not less likely to undergo testing between 2010 and 2012 (aIRR 0.999, 95% CI [0.990, 1.009]) and between 2013 and 2017 (aIRR 0.996, 95% CI [0.990, 1.003]).

Prescription of any antihypertensive medication after a new diagnosis of hypertension

A total of 65,785 (59.0%) individuals were prescribed one or more antihypertensive medications after a new diagnosis of hypertension, which included 34,624 (57.9%) females and 31,164 (59.9%) males. (Table 3) Prior to adjustment, females compared to males, were less likely to be prescribed a antihypertensive medication after a new diagnosis of hypertension (HR 0.96 95% CI [0.94, 0.97]), but adjusted analysis did not show a difference (aHR 0.98, 95% CI [0.96, 0.99]). There was no difference in the number of antihypertensive medications between females and males. The median (IQR) time from index date to time of first prescription was 21 (1-386) days with no significant difference between the sexes (p value 0.053). Compared to males, females were more likely to be prescribed a thiazide/thiazide-like diuretic and less likely to be prescribed other antihypertensives, including hydralazine, clonidine, antiarrhythmics, sodium-glucose transport protein 2 inhibitors, and alpha blockers. There were no differences in

the prescription of ACE inhibitors, ARBs, beta blockers, calcium channel blockers, and nitrates between females and males. (Figure 2)

Older age and period effect of hypertension diagnosis were found to be effect modifiers of the antihypertensive medication prescription after a new diagnosis of hypertension ($p \leq 0.005$). Females were more likely than males to be prescribed medication with increasing age. While females were equally likely to receive treatment between 2010 and 2012 (aHR 0.99, 95% CI [0.97, 1.01]), females were less likely to be prescribed an antihypertensive medication between 2013 and 2017 (aHR 0.97, 95% CI [0.94, 0.98]).

First prescription of antihypertensive medication(s) according to Hypertension Canada guidelines

There were a total of 32,911 (55.4%) females and 28,577 (55.0%) males prescribed a guideline-recommended antihypertensive medication after a new diagnosis of hypertension. Time to prescription of a guideline-recommended antihypertensive medication was not different between sexes (HR 0.995, 95% CI [0.98, 1.01]). Females were significantly less likely to be prescribed a recommended antihypertensive medication (aHR 0.995, 95% CI [0.994, 0.997]) compared to males. Within in the diabetes subgroup ($n=6,502$; 10.6%), there was a significant decrease recommended antihypertensive medication in females (HR 0.98 [0.94, 1.03], aHR 0.99, 95% CI [0.98, 0.99]). There were a total of 3,354 (5.5%) individuals with CAD, comprising 1,212 (36.1%) females and 2,142 (63.9%) males. Compared to males with CAD, females were less likely to be prescribed a recommended antihypertensive medication (HR 0.87 [0.81, 0.94], aHR 0.99, 95% CI [0.98, 0.99]). In the CHF group of 463 (0.76%), females were significantly less likely to be prescribed a recommended antihypertensive medication (HR 0.82 [0.68, 0.99], aHR 0.98, 95% CI [0.96, 0.98]). In the stroke subgroup, which included 176 (41.9%) females and 244 (58.1%) males, there was no difference in the prescription of recommended antihypertensive medications (HR 0.998 [0.82, 1.21], aHR 0.99, 95% CI [0.98, 1.003]).

Discussion

In our population-based cohort study of 111,410 older adults with newly diagnosed hypertension, we found that females had similar rates of testing and completion of guideline-recommended investigations, compared to males. While we found small statistically significant differences prescription rates of appropriate therapies in females compared to males, these differences may be important at the population-level. Statistical differences in prescription of a guideline-recommended medication were consistent across all subgroups of diabetes, CAD, and CHF (but not stroke). Compared to males, females were less likely to undergo testing with increasing age with slight differences in prescriptions observed over time (fewer females prescribed antihypertensive medications more recently) and by age (older females more likely to receive a prescription). Although differences were small, they may have clinical significance at the population level. Our study findings suggest that there are limited sex-based disparities in the initial management of late-onset hypertension.

Our previous research demonstrated that females with late-onset hypertension have reduced risk of adverse cardiovascular outcomes and death compared to males, despite conflicting biologic and epidemiologic concerns that females may experience greater risk of cardiovascular outcomes than men.⁽³⁰⁾ Females are as likely to complete investigations after a new diagnosis of hypertension and almost as likely to be prescribed an any or guideline-recommended antihypertensive medication. The differences in observed outcomes are not explained by differences in initial hypertension care. This also raises the possibility that females benefit more from antihypertensive medication, but this is unclear due to baseline differences in comorbidities among males, lack of data on treatment adherence, and potential residual confounding, including gender-related issues.

The lower antihypertensive medication prescription rate among females, compared to males, was seen with a more recent (2013-2017) hypertension diagnosis but not with an earlier (2010-2012) diagnosis. Despite the small difference, this finding is surprising given the 2016 Hypertension Canada guideline's recommendation for more intensive blood pressure lowering, based on evidence supporting lower treatment targets in older adults.⁽²⁷⁾ In contrast to males,

females were more likely to be prescribed a thiazide/thiazide-like diuretic as their first antihypertensive medication. This may be related to males having more comorbidities necessitating other antihypertensive medication, females having more volume-dependent hypertension, and is consistent with studies that have reported higher prevalent thiazide diuretic use among females or found no difference.^(5, 10, 14) Although literature around the differential use of prevalent antihypertensive medications among the sexes exists, there appears to be an important gap around use of guideline-recommended treatment after incident hypertension diagnosis, which our data begin to fill and which may be an important consideration for assessing quality of care.⁽⁸⁻¹⁵⁾

In contrast to the Ontario Survey Blood Pressure study, where 82% reported taking antihypertensive drugs, our study revealed that many older adults (41%) were not prescribed antihypertensive medications after a new diagnosis of hypertension.⁽³¹⁾ Moreover, while monotherapy and dual therapy were prevalent (51% and 49%), our study showed that 59% of older adults were prescribed one or more antihypertensive medications after a new diagnosis of hypertension, despite a similar distribution of comorbidities.⁽³¹⁾ This finding is of particular concern as the impact of late-onset hypertension on cardiovascular outcomes and mortality is substantial.⁽³⁰⁾ Although lifestyle considerations may have been initially employed, it is likely that a substantial proportion would have required medication during follow-up. This suggests that late-onset hypertension is being untreated despite the evidence for aggressive management and may also reflect potential patient concerns about accepting antihypertensive medication and unwanted drug effects.

Despite Canadian data suggesting higher awareness of their diagnosis, females were not more likely to receive guideline-recommended antihypertensive medication and complete investigations for a new diagnosis of hypertension in our study.⁽³²⁾ Furthermore, assessments in older adults are largely complete, except for urinalysis. It is unclear if this is not performed due to lack of provider orders or patient adherence. Overall, adherence to assessment for a new diagnosis of hypertension is excellent among older adults but kidney injury may be missed

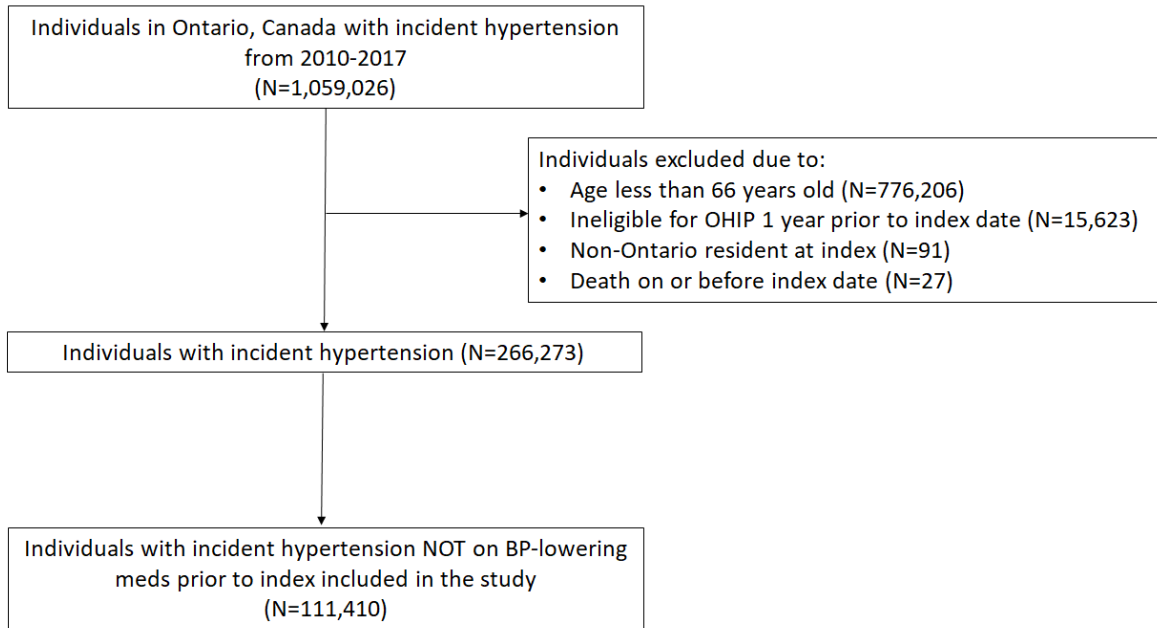
without urinalysis. Importantly, these results not only add to the literature on sex differences in hypertension, but also specifically describe hypertension management in older adults, a rapidly growing, underrepresented population with a significant incidence of hypertension.

While our findings are strengthened by our population-based cohort and consistency across several stratified and subgroup analyses, there are limitations. First, we are unable to confirm generalizability to other health care systems. Second, our results are limited to findings related to sex and cannot be extrapolated to gender. Although existing literature supports the influence of gender as a social construct for hypertension outcomes, most older adults have congruent sex and gender identities.^(10, 12, 13, 32-36) Third, residual confounding may be present. At baseline, males had a higher prevalence of diabetes, CAD, and cancer compared to females, but this did not lead to an increased likelihood of testing among males. We were unable to differentiate between non-dihydropyridine and dihydropyridine calcium channel blockers. However, this limitation would only potentially impact results for the subgroup with diabetes, where the dihydropyridine subtype is specified. Blood pressure measurement data, smoking, body mass index, and ethnicity were not available in our dataset but are not expected to impact first prescription of antihypertensive medication or performance of laboratory investigations. Lastly, while blood pressure measurement and adverse drug event data were unavailable, we focused on the first prescription of an antihypertensive medication in a cohort that was not on any antihypertensive medication within one year prior to their index date.

In conclusion, in our population-level study of care processes in late-onset hypertension, we found that only 59% receive antihypertensive therapy. There were no sex-specific differences in the performance of guideline-recommended investigations and no clinically meaningful differences in the prescription of antihypertensive medication. Further studies are needed to elucidate factors leading to sex-based differences in cardiovascular outcomes and mortality, given that it may not be directly linked to the hypertension care delivery.

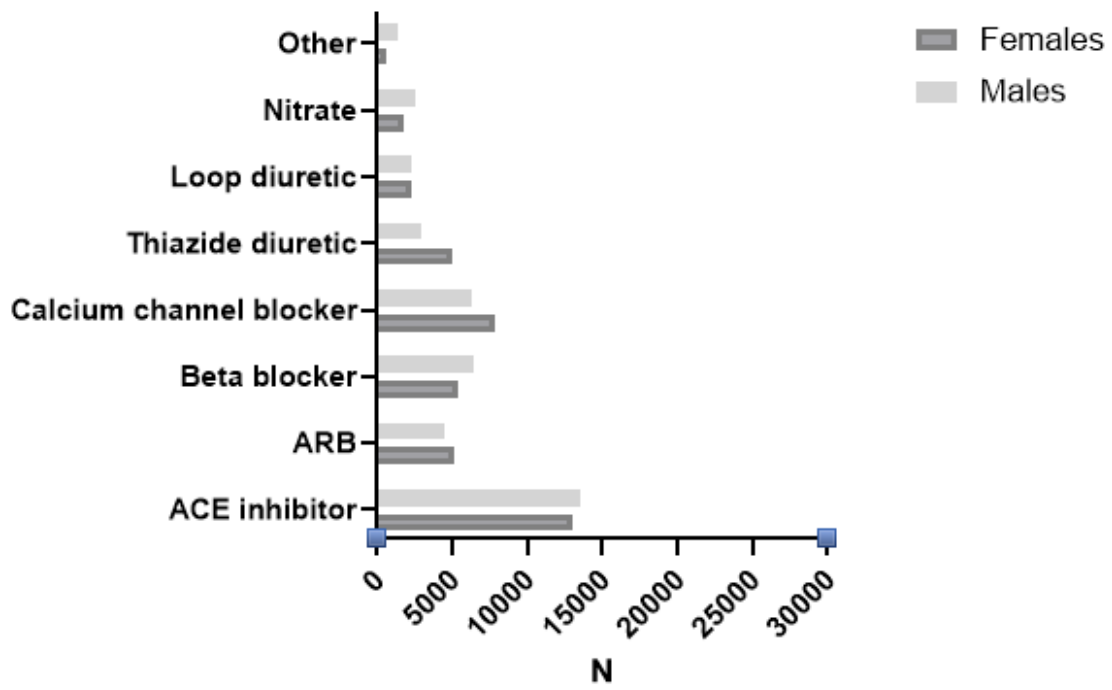
FIGURES (Chapter 4)

Figure 1. Flow Diagram for Cohort Assembly



OHIP refers to Ontario Health Insurance Plan

Figure 2. Distribution of antihypertensive medications.



TABLES (Chapter 4)

Table 1. Baseline characteristics among individuals with a new diagnosis of hypertension by sex

| | Complete cohort N=111,410 | Female N=59,422 | Male N=51,988 | St. diff |
|--|--------------------------------------|----------------------------|--------------------------|-----------------|
| Age, y, mean (SD) | 73 (7) | 74 (7) | 73 (6) | 0.09 |
| Follow-up duration in years, median (IQR) | 6.8 (4.8-9.2) | 7.0 (5.0-9.3) | 6.6 (4.7-9.0) | |
| Total no. of person years of follow-up | 136.0 | 74.3 | 61.7 | |
| Income Quintile | | | | |
| Quintile 1: lowest | 20697 (18.6) | 11399 (19.2) | 9298 (17.9) | 0.03 |
| Quintile 2 | 22387 (20.1) | 12154 (20.4) | 10233 (19.7) | 0.02 |
| Quintile 3 | 22084 (19.8) | 11724 (19.7) | 10360 (19.9) | 0.01 |
| Quintile 4 | 22313 (20.0) | 11686 (19.7) | 10627 (20.4) | 0.02 |
| Quintile 5: highest | 23929 (21.5) | 12459 (21.0) | 11470 (22.1)) | 0.03 |
| Era of hypertension diagnosis | | | | |
| 2010-2012 | 42,101 (37.8) | 22,918 (38.6) | 19,183(36.9) | 0.04 |
| 2013-2017 | 69,309 (62.2) | 36,504 (61.4) | 32,805 (63.1) | 0.04 |
| Rural residence | 12,244 (11.0) | 6,026 (10.1) | 6,218 (12.0) | 0.06 |
| Comorbid conditions within 3 years of index | | | | |
| Coronary artery disease | 5719 (5.1) | 2149 (3.6) | 3570 (6.9) | 0.15 |
| Myocardial infarction | 1323 (1.2) | 429 (0.72) | 894 (1.72) | 0.09 |
| Coronary artery bypass graft | 391 (0.35) | 135 (0.23) | 256 (0.49) | 0.04 |
| Congestive heart failure | 907 (0.81) | 524 (0.88) | 383 (0.74) | 0.02 |
| Atrial fibrillation | 1335 (1.2) | 575 (1.0) | 760 (1.5) | 0.05 |
| Arrhythmia | 2295 (2.1) | 994 (1.7) | 1301 (2.5) | 0.06 |
| Ischemic stroke | 994 (0.9) | 415 (0.7) | 579 (1.1) | 0.04 |
| Peripheral vascular disease | 606 (0.5) | 184 (0.3) | 422 (0.8) | 0.07 |
| Diabetes | 12585 (11.3) | 5703 (9.6) | 6882 (13.2) | 0.11 |
| Chronic obstructive pulmonary disease | 2349 (2.1) | 1176 (2.0) | 1173 (2.3) | 0.02 |
| Chronic liver disease | 1438 (1.3) | 648 (1.1) | 790 (1.5) | 0.04 |
| Major cancer | 9839 (8.8) | 3940 (6.6) | 5899 (11.4) | 0.17 |
| Seizure | 311 (0.3) | 144 (0.2) | 167 (0.3) | 0.02 |
| Osteoporosis | 332 (0.3) | 279 (0.5) | 53 (0.1) | 0.07 |
| Chronic renal disease | 420 (0.4) | 152 (0.3) | 268 (0.5) | 0.03 |
| Dementia | 1483 (1.3) | 830 (1.4) | 653 (1.3) | 0.01 |
| Health Services | | | | |
| Family physician visits (median, IQR) | 5(2-8) | 5(3-8) | 5(2-8) | |
| ED visits (median, IQR) | 0(1) | 0(1) | 0(1) | |
| Hospitalizations (median, IQR) | 0(1) | 0(1) | 0(1) | |

Values are number (percentage), unless specified as mean (standard deviation (SD)) or median (interquartile range).

Table 2. Investigations performed for new diagnosis of hypertension as per Hypertension Canada Guidelines within 1 year of index date

| Investigation | Event Frequency (N/%) | Unadjusted relative effect* (95% CI) | Adjusted relative effect* (95% CI) |
|---|------------------------|--------------------------------------|------------------------------------|
| At least 1 investigation performed | 107,750/111,410 (96.7) | | |
| Female | 57,504/59,422 (96.8) | 0.99 (0.98, 0.99) | 0.997 (0.99, 1.002) |
| Male | 50,246/51,988 (96.7) | ref | ref |
| All investigations performed | 813/111,410 (0.73) | | |
| Female | 414/59,422 (0.70) | 0.91 (0.79, 1.04) | 0.96 (0.83, 1.11) |
| Male | 399/51,988 (0.77) | ref | ref |

Values are number (percentage), unless specified as mean (standard deviation).

*Relative effect refers to incidence rate ratio for having at least 1 investigation performed and odds ratio for having all seven recommended investigations performed.

Table 3. Antihypertensive medications after new diagnosis of hypertension

| | Complete cohort N=111,410 | Female N=59,422 | Male N=51,988 | St. diff |
|---|--------------------------------------|----------------------------|--------------------------|-----------------|
| No. of BP-lowering medications | | | | |
| 0 | 45,625 (41.0) | 24,798 (41.7) | 20,827 (40.1) | 0.03 |
| 1 | 55,399 (49.7) | 30,042 (50.6) | 25,357 (48.8) | 0.04 |
| 2 | 7,239 (6.5) | 3,302 (5.6) | 3,937 (7.6) | 0.08 |
| 3 | 2,573 (2.3) | 1,041 (1.8) | 1,532 (3.0) | 0.08 |
| 4 | 500 (0.4) | 198 (0.3) | 302 (0.6) | 0.04 |
| 5+ | 74 (0.09) | 41 (0.07) | 33 (0.06) | 0.00 |
| | | | | |
| Time from index to time of first prescription, median (IQR) days | 21 (1-286) | 22 (1-309) | 21 (1-265) | |
| | | | | |
| Medications | | | | |
| Angiotensin converting enzyme inhibitor | 26,523 (23.8) | 13,019 (21.9) | 13,504 (26.0) | 0.10 |
| Angiotensin receptor blocker | 9,508 (8.5) | 5,075 (8.5) | 4,433 (8.5) | 0.10 |
| Beta blocker | 11,816 (10.6) | 5,423 (9.1) | 6,393 (12.3) | 0.10 |
| Calcium channel blocker | 14,233 (12.8) | 7,905 (13.3) | 6,328 (12.2) | 0.03 |
| Thiazide diuretic | 8,008 (71.9) | 5,050 (8.5) | 2,958 (5.7) | 0.11 |
| Loop diuretic | 4,605 (4.1) | 2,273 (3.8) | 2,332 (4.5) | 0.04 |
| Nitrate | 4,351 (3.9) | 1,787 (3.0) | 2,564 (4.9) | 0.10 |
| Other* | 1,928 (1.7) | 610 (1.0) | 1,318 (9.8) | 0.40 |

BP refers to blood pressure.

Values are number (percentage), unless specified as median (interquartile range). Individuals can be counted more than once if they were prescribed more than 1 medication after diagnosis.

Other: alpha-blocker, hydralazine, clonidine, antiarrhythmic, sodium-glucose cotransporter-2 inhibitor

CHAPTER 5: DISCUSSION

Summary of thesis

This thesis investigates cardiovascular outcomes and care processes in an older adult population newly diagnosed with hypertension, using linked provincial health administrative databases. In Chapter 2 we provided background information about the clinical significance of hypertension and highlighted sex-based differences in its pathophysiology, epidemiology, management, and outcomes. In Chapter 3 (Manuscript 1), we estimated the risk of all-cause death, cardiovascular death, and cardiovascular outcome (a composite outcome of nonfatal myocardial infarction, nonfatal stroke, and congestive heart failure) by sex, using time to event analyses in both the overall cohort and key clinical subgroups. Lastly, in Chapter 4 (Manuscript 2), we used Poisson and logistic regression to estimate adjusted sex-attributable differences in the performance of guideline-recommended lab investigations. Furthermore, we estimated adjusted differences in time to the prescription of first antihypertensive medication and the type of medication prescribed between females and males, using Cox regression. This discussion chapter will highlight the novel findings, explore their implications for managing late-onset hypertension, and evaluate the strengths and limitations of the two manuscripts. Additionally, we will outline future avenues of research.

Novel findings

We found that a quarter of older adults received a new diagnosis of hypertension. Female sex may be associated with a lower risk of adverse outcomes, including all-cause death, cardiovascular death, and cardiovascular events, compared to older males. However, older females were almost as likely as older males to complete guideline-recommended investigations for hypertension and be prescribed guideline-recommended, first-line antihypertensive medication.

In Manuscript 1, we reported that the risk of the primary composite cardiovascular outcome (myocardial infarction, stroke, and congestive heart failure) was lower among females (adjusted

hazard ratio [aHR], 0.75 [95% CI 0.73 to 0.76]; $p < 0.001$) than in males. This was consistent after adjusting for the competing risk of all-cause death with a sub-distributional hazard ratio of 0.88 (95% CI [0.86 to 0.91]; $p < 0.001$). Females had a lower risk all-cause death compared to males (aHR 0.72, 95% CI [0.71, 0.73]) and a lower risk of cardiovascular death (aHR 0.85, 95% CI [0.82, 0.99]). Females had a lower risk of undergoing a revascularization procedure, compared to males, (aHR 0.91, 95% CI [0.89, 0.94]), even after accounting for all-cause death (sHR 0.47, 95% CI [0.46, 0.49]) and cardiovascular death (sHR 0.45 95% CI [0.43, 0.46]). These findings persisted in stratified analyses by both pre-existing diabetes and pre-existing prescription of blood pressure-lowering medication.

We examined care processes to account for these differences in outcomes by sex in Manuscript 2 and found that less than half of all patients (41%) received antihypertensive therapy. Females underwent a similar number of guideline-recommended investigations (adjusted incidence rate ratio, 0.997 [95% CI 0.99 to 1.002]) compared to males. Females were slightly less likely to be prescribed an antihypertensive medication than males (aHR 0.98 [95% CI 0.96 to 0.99]). Among those prescribed medication, females were slightly less likely to be prescribed *guideline-recommended first-line* medication (aHR, 0.995 [95% CI 0.994 to 0.997]). These small but statistically significant differences persisted across all subgroups with diabetes, coronary artery disease, and congestive heart failure, but not stroke. While males had more comorbidity at baseline, this did not lead to increased likelihood of testing but may have contributed to their worse outcomes. Residual confounding may be present as we did not have blood pressure measurement, smoking and body mass or waist circumference data.

Implications for clinical practice

Our findings from a contemporary, population-based sample of older adults with new, incident hypertension reveal several implications for clinical practice. First, a meaningful number of older adults with newly diagnosed hypertension are not receiving treatment, and amongst those who do initiate therapy, opportunities exist to improve guideline adherence with treatment. While most recommended evaluations were completed, few patients undergo

urinalysis, which could reduce patients' and providers' abilities to identify hypertension-related kidney injury. Lastly, among older males with newly diagnosed hypertension, adjusted rates of major adverse cardiac events were significantly higher than among females, which may require greater focus on Hypertension Canada guidelines by care providers.

A large proportion of older adults with incident hypertension are not prescribed antihypertensive therapy despite the 2016 Hypertension Canada guideline's recommendation for more intensive blood pressure lowering.⁽⁶³⁾ Current guidelines notably lack specific provisions addressing the importance of managing hypertension in older adults, a rapidly growing demographic with a high incidence of new onset hypertension. For patients, providers and the health care system should aim to highlight hypertension's often asymptomatic nature and the adverse cardiovascular outcomes that can result from unmanaged hypertension. Improving patient, provider and system-level focus on gaps in the pharmacologic management of hypertension can improve treatment rates.

Awareness of sex-specific disparities is important for informing clinical practice. First, females are slightly less likely than males to be prescribed the recommended first-line antihypertensive medication. Next, older females are more likely than older males to be prescribed medication with increasing age. Lastly, females are less likely to be prescribed an antihypertensive medication with a more recent hypertension diagnosis and with pre-existing comorbidities. Attention to sex-related disparities, acknowledging that differences may also be gender-related, at the provider and system-level may improve adherence to guideline recommendations and cardiovascular outcomes.

Investigations performed for a new diagnosis of hypertension commonly omit urinalysis. Clarifying the rationale for urinalysis to detect kidney injury in the guidelines, communicating the rationale to patients, and making urine collection simple (such as facilitating home-based collection and removing barriers to delivery to laboratory facilities) may improve performance.

To comprehensively understand the mechanisms for the apparent higher risk of cardiovascular outcomes among males, data on medication adherence, medication changes, and blood pressure control are required. Studies using mixed methods can offer insights by examining blood pressure control and medication use and adherence as well as qualitative aspects, such as gender identities and gender roles. Understanding how antihypertensive medication use and gender influence hypertension management is necessary to improve cardiovascular outcomes.

Limitations

While our findings are strengthened by use of population-based data, validated codes to identify cohort inclusion, and consistency across stratified analyses, it also has limitations. At baseline, males had a higher prevalence of diabetes, coronary artery disease, and cancer compared to females, potentially impacting outcomes. Despite males having more comorbidities, they were not more likely to undergo testing. While consistently demonstrating a lower risk of cardiovascular outcomes and death for females in all analyses, we cannot comment on difference in outcomes based on the degree of hypertension treatment between the sexes or biological mechanisms. Blood pressure measurement and adverse drug event data were unavailable, so we focused on the first prescription of an antihypertensive medication in a cohort that was not on any antihypertensive medication within one year prior to their index date. Our findings are limited to sex-based findings and cannot be extrapolated to gender, although there is a strong literature base on the influence of gender as a social construct for hypertension outcomes.(11, 18, 49, 51, 52, 67) We also lacked the racial and ethnic composition of our cohort. Sex-specific factors around menopausal and reproductive history were not captured, such as gestational hypertension and pre-eclampsia, that may predispose females to hypertension later in life. Body mass index or waist circumference measurements, cholesterol data, and smoking status were unavailable in our datasets. As smoking is a risk factor for cardiovascular outcomes and death, and is more common among males, this would serve as a potential confounder.(74) Residual confounding may be present, including treatment adherence and blood pressure control. Finally, the scope of this thesis is restricted to a single health care system, necessitating comprehensive local and regional data for targeted

hypertension management.

Further research avenues

Given the high incidence of hypertension in this patient cohort, future studies should identify potential mechanisms for sex-based differences in mortality and cardiovascular outcomes in older adults. This includes examining blood pressure control, antihypertensive medication changes over time and adherence to therapy, all of which can impact outcomes. It is also crucial to explore the impact of potential gender roles on hypertension outcomes as females in the workforce, contraception use, birth timing, and birth rates have changed over time. This approach will promote targeted and personalized approaches to hypertension management and optimize clinical outcomes in both sexes, given that it may not be directly linked to hypertension care delivery. Furthermore, it is important to examine kidney outcomes related to new-onset hypertension, including albuminuria, major changes in kidney function over time and the need for kidney replacement therapy (dialysis or transplantation) as the presence of these outcomes is associated with cardiovascular disease, cardiovascular death, and all-cause death. Finally, it would be beneficial to examine outcomes and management of late-onset hypertension in newly arrived immigrants to ensure that there are no disparities in this group as a recent, large Canadian study has shown that white older immigrants were 35% more likely to report being in good health than racialized immigrants.(75)

Conclusion

Among a population-based cohort of older adults in Ontario, one quarter developed new-onset hypertension. Compared to males, females had a lower risk of cardiovascular outcomes, despite previous estimates from non-risk adjusted cohorts and studies of younger adults suggesting otherwise. (10, 11, 70, 71) These findings persisted after adjustment for the competing risk of all-cause death and in stratified analyses by both pre-existing diabetes and pre-existing presence of antihypertensive medication. Compared to males, females with newly diagnosed late-onset hypertension were equally likely to complete initial investigations with

comparable prescription of appropriate therapies. Females were also slightly less likely to be prescribed an antihypertensive medication, or among those prescribed, slightly less likely to be prescribed guideline-recommended first-line medication, as compared to males. These small but statistically significant differences persisted across subgroups with diabetes, coronary artery disease, and congestive heart failure. These findings suggest that there may be no clinically meaningful sex-based differences in the initial management of late-onset hypertension to explain sex-based disparities in cardiovascular outcomes.

References

1. Vogel B, Acevedo M, Appelman Y, Bairey Merz CN, Chieffo A, Figtree GA, et al. The Lancet women and cardiovascular disease Commission: reducing the global burden by 2030. *Lancet*. 2021;397(10292):2385-438.
2. Padwal RS, Bienek A, McAlister FA, Campbell NR. Epidemiology of Hypertension in Canada: An Update. *Can J Cardiol*. 2016;32(5):687-94.
3. Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. *Nat Rev Nephrol*. 2020;16(4):223-37.
4. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet*. 2016;387(10022):957-67.
5. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. *Circulation*. 2019;139(10):e56-e528.
6. Yusuf S, Joseph P, Rangarajan S, Islam S, Mentz A, Hystad P, et al. Modifiable risk factors, cardiovascular disease, and mortality in 155 722 individuals from 21 high-income, middle-income, and low-income countries (PURE): a prospective cohort study. *Lancet*. 2020;395(10226):795-808.
7. Wang C, Yuan Y, Zheng M, Pan A, Wang M, Zhao M, et al. Association of Age of Onset of Hypertension With Cardiovascular Diseases and Mortality. *Journal of the American College of Cardiology*. 2020;75(23):2921-30.
8. Rana J, Oldroyd J, Islam MM, Tarazona-Meza CE, Islam RM. Prevalence of hypertension and controlled hypertension among United States adults: Evidence from NHANES 2017-18 survey. *Int J Cardiol Hypertens*. 2020;7:100061.
9. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. *Jama*. 1996;275(20):1557-62.
10. Boggia J, Thijs L, Hansen TW, Li Y, Kikuya M, Björklund-Bodegård K, et al. Ambulatory blood pressure monitoring in 9357 subjects from 11 populations highlights missed opportunities for cardiovascular prevention in women. *Hypertension*. 2011;57(3):397-405.
11. Wenger NK, Arnold A, Bairey Merz CN, Cooper-DeHoff RM, Ferdinand KC, Fleg JL, et al. Hypertension Across a Woman's Life Cycle. *J Am Coll Cardiol*. 2018;71(16):1797-813.
12. Colafella KMM, Denton KM. Sex-specific differences in hypertension and associated cardiovascular disease. *Nat Rev Nephrol*. 2018;14(3):185-201.
13. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2019 (GBD 2019) results. Seattle, WA, USA: Institute for Health Metrics and Evaluation, 2020. <http://ghdx.healthdata.org/gbd-results-tool> (accessed April 29, 2024). [
14. Weaver CG, Clement FM, Campbell NR, James MT, Klarenbach SW, Hemmelgarn BR, et al. Healthcare Costs Attributable to Hypertension: Canadian Population-Based Cohort Study. *Hypertension*. 2015;66(3):502-8.
15. Garies S, Hao S, McBrien K, Williamson T, Peng M, Khan NA, et al. Prevalence of Hypertension, Treatment, and Blood Pressure Targets in Canada Associated With the 2017 American College of Cardiology and American Heart Association Blood Pressure Guidelines. *JAMA Netw Open*. 2019;2(3):e190406.
16. Hackam DG, Khan NA, Hemmelgarn BR, Rabkin SW, Touyz RM, Campbell NR, et al. The 2010 Canadian Hypertension Education Program recommendations for the management of hypertension: part

2 - therapy. *Can J Cardiol.* 2010;26(5):249-58.

17. Tominaga T, Suzuki H, Ogata Y, Matsukawa S, Saruta T. The role of sex hormones and sodium intake in postmenopausal hypertension. *J Hum Hypertens.* 1991;5(6):495-500.

18. Connelly PJ, Currie G, Delles C. Sex Differences in the Prevalence, Outcomes and Management of Hypertension. *Curr Hypertens Rep.* 2022.

19. Miller VM, Harman SM. An update on hormone therapy in postmenopausal women: mini-review for the basic scientist. *Am J Physiol Heart Circ Physiol.* 2017;313(5):H1013-h21.

20. Kantarci K, Tosakulwong N, Lesnick TG, Kara F, Kendall-Thomas J, Kapoor E, et al. Cardiometabolic outcomes in Kronos Early Estrogen Prevention Study continuation: 14-year follow-up of a hormone therapy trial. *Menopause.* 2024;31(1):10-7.

21. Huby AC, Otvos L, Jr., Belin de Chantemèle EJ. Leptin Induces Hypertension and Endothelial Dysfunction via Aldosterone-Dependent Mechanisms in Obese Female Mice. *Hypertension.* 2016;67(5):1020-8.

22. Statistics Canada. <https://www150.statcan.gc.ca/n1/pub/82-003-x/2019002/article/00001/tbl/tbl01-eng.htm>, accessed May 13, 2024 [

23. Bugeja A, Girard C, Sood MM, Kendall CE, Sweet A, Singla R, et al. Sex-Related Disparities in Cardiovascular Outcomes Among Older Adults With Late-Onset Hypertension. *Hypertension.* 2024.

24. Benetos A, Petrovic M, Strandberg T. Hypertension Management in Older and Frail Older Patients. *Circ Res.* 2019;124(7):1045-60.

25. Pana TA, Luben RN, Mamas MA, Potter JF, Wareham NJ, Khaw KT, et al. Long Term Prognostic Impact of Sex-specific Longitudinal Changes in Blood Pressure. The EPIC-Norfolk Prospective Population Cohort Study. *Eur J Prev Cardiol.* 2022;29(1):180-91.

26. Chu SH, Baek JW, Kim ES, Stefani KM, Lee WJ, Park YR, et al. Gender differences in hypertension control among older korean adults: Korean social life, health, and aging project. *J Prev Med Public Health.* 2015;48(1):38-47.

27. Keyhani S, Scobie JV, Hebert PL, McLaughlin MA. Gender disparities in blood pressure control and cardiovascular care in a national sample of ambulatory care visits. *Hypertension.* 2008;51(4):1149-55.

28. Zhao M, Woodward M, Vaartjes I, Millett ERC, Klipstein-Grobusch K, Hyun K, et al. Sex Differences in Cardiovascular Medication Prescription in Primary Care: A Systematic Review and Meta-Analysis. *J Am Heart Assoc.* 2020;9(11):e014742.

29. August P, Oparil S. Hypertension in women. *J Clin Endocrinol Metab.* 1999;84(6):1862-6.

30. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet.* 2002;360(9349):1903-13.

31. Haring B, Andrews CA, Hovey K, Shadyab AH, LaCroix A, Martin LW, et al. Systolic Blood Pressure and Survival to Very Old Age: Results From the Women's Health Initiative. *Circulation.* 2024.

32. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet.* 2004;364(9438):937-52.

33. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. *N Engl J Med.* 2001;344(1):3-10.

34. Wright JT, Jr., Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *N Engl J Med.* 2015;373(22):2103-16.

35. Margolis KL, O'Connor PJ, Morgan TM, Buse JB, Cohen RM, Cushman WC, et al. Outcomes of combined cardiovascular risk factor management strategies in type 2 diabetes: the ACCORD randomized trial. *Diabetes Care.* 2014;37(6):1721-8.

36. Ambrosius WT, Sink KM, Foy CG, Berlowitz DR, Cheung AK, Cushman WC, et al. The design and

rationale of a multicenter clinical trial comparing two strategies for control of systolic blood pressure: the Systolic Blood Pressure Intervention Trial (SPRINT). *Clin Trials*. 2014;11(5):532-46.

37. Os I, Franco V, Kjeldsen SE, Manhem K, Devereux RB, Gerds E, et al. Effects of losartan in women with hypertension and left ventricular hypertrophy: results from the Losartan Intervention for Endpoint Reduction in Hypertension Study. *Hypertension*. 2008;51(4):1103-8.

38. Wing LM, Reid CM, Ryan P, Beilin LJ, Brown MA, Jennings GL, et al. A comparison of outcomes with angiotensin-converting--enzyme inhibitors and diuretics for hypertension in the elderly. *N Engl J Med*. 2003;348(7):583-92.

39. Kjeldsen SE, Hedner T, Syvertsen JO, Lund-Johansen P, Hansson L, Lanke J, et al. Influence of age, sex and blood pressure on the principal endpoints of the Nordic Diltiazem (NORDIL) Study. *J Hypertens*. 2002;20(6):1231-7.

40. Kjeldsen SE, Warnold I, Hansson L. Influence of gender on prevention of myocardial infarction by antihypertensives and acetylsalicylic acid: the HOT study. *J Gend Specif Med*. 2000;3(8):35-8.

41. Neaton JD, Grimm RH, Jr., Prineas RJ, Stamler J, Grandits GA, Elmer PJ, et al. Treatment of Mild Hypertension Study. Final results. Treatment of Mild Hypertension Study Research Group. *Jama*. 1993;270(6):713-24.

42. Lewis CE, Grandits A, Flack J, McDonald R, Elmer PJ. Efficacy and tolerance of antihypertensive treatment in men and women with stage 1 diastolic hypertension. Results of the Treatment of Mild Hypertension Study. *Arch Intern Med*. 1996;156(4):377-85.

43. Turnbull F, Woodward M, Neal B, Barzi F, Ninomiya T, Chalmers J, et al. Do men and women respond differently to blood pressure-lowering treatment? Results of prospectively designed overviews of randomized trials. *Eur Heart J*. 2008;29(21):2669-80.

44. Parry M, Van Spall HGC, Mullen KA, Mulvagh SL, Pacheco C, Colella TJF, et al. The Canadian Women's Heart Health Alliance Atlas on the Epidemiology, Diagnosis, and Management of Cardiovascular Disease in Women - Chapter 6: Sex- and Gender-Specific Diagnosis and Treatment. *CJC Open*. 2022;4(7):589-608.

45. Chang DH, Dumanski SM, Ahmed SB. Female sex-specific considerations to improve rigor and reproducibility in cardiovascular research. *Am J Physiol Heart Circ Physiol*. 2023;324(3):H279-h87.

46. Yang J, Wu S, Wang A, Chen S, Yang C, Zhang Q. Sex-specific risk factors for early-onset ischaemic stroke. *Eur J Neurosci*. 2023;57(10):1763-74.

47. Mosca L, Benjamin EJ, Berra K, Bezanson JL, Dolor RJ, Lloyd-Jones DM, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women--2011 update: a guideline from the American Heart Association. *Circulation*. 2011;123(11):1243-62.

48. Ahmad A, Oparil S. Hypertension in Women: Recent Advances and Lingering Questions. *Hypertension*. 2017;70(1):19-26.

49. Osude N, Durazo-Arvizu R, Markossian T, Liu K, Michos ED, Rakotz M, et al. Age and sex disparities in hypertension control: The multi-ethnic study of atherosclerosis (MESA). *Am J Prev Cardiol*. 2021;8:100230.

50. Gu Q, Burt VL, Paulose-Ram R, Dillon CF. Gender differences in hypertension treatment, drug utilization patterns, and blood pressure control among US adults with hypertension: data from the National Health and Nutrition Examination Survey 1999-2004. *Am J Hypertens*. 2008;21(7):789-98.

51. Bager JE, Manhem K, Andersson T, Hjerpe P, Bengtsson-Boström K, Ljungman C, et al. Hypertension: sex-related differences in drug treatment, prevalence and blood pressure control in primary care. *J Hum Hypertens*. 2023;37(8):662-70.

52. Joo HJ, Yum Y, Kim YH, Son JW, Kim SH, Choi S, et al. Gender Difference of Blood Pressure Control Rate and Clinical Prognosis in Patients With Resistant Hypertension: Real-World Observation Study. *J Korean Med Sci*. 2023;38(16):e124.

53. Ljungman C, Kahan T, Schiöler L, Hjerpe P, Hasselström J, Wettermark B, et al. Gender differences

in antihypertensive drug treatment: results from the Swedish Primary Care Cardiovascular Database (SPCCD). *J Am Soc Hypertens*. 2014;8(12):882-90.

54. Levy AR, O'Brien BJ, Sellors C, Grootendorst P, Willison D. Coding accuracy of administrative drug claims in the Ontario Drug Benefit database. *Can J Clin Pharmacol*. 2003;10(2):67-71.

55. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. *Med Care*. 1998;36(1):8-27.

56. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care*. 2005;43(11):1130-9.

57. Tu JV, Chu A, Donovan LR, Ko DT, Booth GL, Tu K, et al. The Cardiovascular Health in Ambulatory Care Research Team (CANHEART): using big data to measure and improve cardiovascular health and healthcare services. *Circ Cardiovasc Qual Outcomes*. 2015;8(2):204-12.

58. Davidson J, Banerjee A, Muzambi R, Smeeth L, Warren-Gash C. Validity of Acute Cardiovascular Outcome Diagnoses Recorded in European Electronic Health Records: A Systematic Review. *Clin Epidemiol*. 2020;12:1095-111.

59. Saunders-Hastings P, Heong SW, Srichaikul J, Wong HL, Shoaibi A, Chada K, et al. Acute myocardial infarction: Development and application of an ICD-10-CM-based algorithm to a large U.S. healthcare claims-based database. *PLoS One*. 2021;16(7):e0253580.

60. Pocobelli G, Ichikawa L, Yu O, Green BB, Meyers K, Gray R, et al. Validation of international classification of diseases, tenth revision, clinical modification diagnosis codes for heart failure subtypes. *Pharmacoepidemiol Drug Saf*. 2022;31(9):992-7.

61. McCormick N, Lacaille D, Bhole V, Avina-Zubieta JA. Validity of heart failure diagnoses in administrative databases: a systematic review and meta-analysis. *PLoS One*. 2014;9(8):e104519.

62. Quan H, Khan N, Hemmelgarn BR, Tu K, Chen G, Campbell N, et al. Validation of a case definition to define hypertension using administrative data. *Hypertension*. 2009;54(6):1423-8.

63. Leung AA, Nerenberg K, Daskalopoulou SS, McBrien K, Zarnke KB, Dasgupta K, et al. Hypertension Canada's 2016 Canadian Hypertension Education Program Guidelines for Blood Pressure Measurement, Diagnosis, Assessment of Risk, Prevention, and Treatment of Hypertension. *Can J Cardiol*. 2016;32(5):569-88.

64. Austin PC.

65. Austin PC, Lee DS, Fine JP. Introduction to the Analysis of Survival Data in the Presence of Competing Risks. *Circulation*. 2016;133(6):601-9.

66. McInnis NH, Fodor G, Moy Lum-Kwong M, Leenen FHH. Antihypertensive Medication Use and Blood Pressure Control: A Community-Based Cross-Sectional Survey (ON-BP). *American Journal of Hypertension*. 2008;21(11):1210-5.

67. Leung AA, Williams JVA, McAlister FA, Campbell NRC, Padwal RS. Worsening Hypertension Awareness, Treatment, and Control Rates in Canadian Women Between 2007 and 2017. *Can J Cardiol*. 2020;36(5):732-9.

68. Chaturvedi A, Zhu A, Gadela NV, Prabhakaran D, Jafar TH. Social Determinants of Health and Disparities in Hypertension and Cardiovascular Diseases. *Hypertension*. 2024;81(3):387-99.

69. Nelson C, Fredriksen-Goldsen K, Hoy-Ellis C, Romanelli M, Kim H-J. SEXUAL AND GENDER IDENTITY AND THEIR PROPERTIES IN AGING WITH PRIDE: NATIONAL HEALTH, AGING, AND SEXUALITY AND GENDER STUDY. *Innovation in Aging*. 2023;7(Supplement_1):213-4.

70. Turnbull F, Woodward M, Anna V. Effectiveness of blood pressure lowering: evidence-based comparisons between men and women. *Expert Rev Cardiovasc Ther*. 2010;8(2):199-209.

71. Hermida RC, Ayala DE, Mojón A, Fontao MJ, Chayán L, Fernández JR. Differences between men and women in ambulatory blood pressure thresholds for diagnosis of hypertension based on cardiovascular outcomes. *Chronobiol Int*. 2013;30(1-2):221-32.

72. Holt E, Joyce C, Dornelles A, Morisky D, Webber LS, Muntner P, et al. Sex differences in barriers to

antihypertensive medication adherence: findings from the cohort study of medication adherence among older adults. *J Am Geriatr Soc.* 2013;61(4):558-64.

73. Tsiantou V, Pantzou P, Pavi E, Koulierakis G, Kyriopoulos J. Factors affecting adherence to antihypertensive medication in Greece: results from a qualitative study. *Patient Preference and Adherence.* 2010;4(null):335-43.

74. Higgins ST, Kurti AN, Redner R, White TJ, Gaalema DE, Roberts ME, et al. A literature review on prevalence of gender differences and intersections with other vulnerabilities to tobacco use in the United States, 2004-2014. *Prev Med.* 2015;80:89-100.

75. McAlpine AA, George U, Kobayashi K, Fuller-Thomson E. Physical Health of Older Canadians: Do Intersections Between Immigrant and Refugee Status, Racialized Status, and Socioeconomic Position Matter? *Int J Aging Hum Dev.* 2022;95(3):326-48.

THESIS SUPPLEMENTARY MATERIAL

SUPPLEMENTARY MATERIAL FOR CHAPTER 3

Supplemental Table S1. Checklist of recommendations for reporting of observational studies using the REporting of studies Conducting using Observational Routinely collected health Data (RECORD) Statement.

| | Item No. | STROBE items | Location in manuscript where items are reported (pages) | RECORD items | Location in manuscript where items are 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 | 1,3,4 | RECORD 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. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract. | 3,4 |
| Introduction | | | | | |

| | | | | | |
|----------------------|---|---|-----|----------------------------------|--|
| Background rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 5,6 | | |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 6 | | |
| Methods | | | | | |
| Study Design | 4 | Present key elements of study design early in the paper | 6 | | |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 6,7 | | |
| Participants | 6 | (a) Cohort study - Give the | 7,8 | RECORD 6.1: The methods of study | 7,8,9 Figure 1 Supplemental material |
| | | | | | |

| | | | | |
|--|---|--|---|--|
| | <p>eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up</p> <p><i>Case-control study</i> - 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</p> <p><i>Cross-sectional study</i> - Give the eligibility criteria, and the sources and methods of selection of participants</p> <p><i>(b) Cohort study</i> - For matched studies, give matching criteria and number of exposed and unexposed</p> <p><i>Case-control study</i> - For matched studies, give matching criteria and the number of</p> | | <p>population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided.</p> <p>RECORD 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.</p> <p>RECORD 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.</p> | |
|--|---|--|---|--|

| | | | | | |
|------------------------------|---|--|-------|---|-----------------------|
| | | controls per case | | | |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable. | 7,8 | RECORD 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. | Supplemental Material |
| Data sources/ measurement | 8 | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment | 6,7,8 | | |

| | | | | | |
|------------------------|----|--|----------|--|--|
| | | methods if there is more than one group | | | |
| Bias | 9 | Describe any efforts to address potential sources of bias | 7 | | |
| Study size | 10 | Explain how the study size was arrived at | Figure 1 | | |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why | 8,9 | | |
| 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- | 8,9 | | |

| | | | | |
|----------------------------------|----|--|---|-----------------|
| | | <p>up was addressed</p> <p>Case-control study - If applicable, explain how matching of cases and controls was addressed</p> <p>Cross-sectional study - If applicable, describe analytical methods taking account of sampling strategy</p> <p>(e) Describe any sensitivity analyses</p> | | |
| Data access and cleaning methods | .. | | <p>RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.</p> <p>RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.</p> | 6,7 Figure 1 |
| Linkage | .. | | RECORD 12.3: State whether the | 6,7 |

Supplemental Table S2. Databases and coding definitions for inclusion and exclusion criteria, outcomes, and baseline characteristics.

| Characteristic/Condition | Database | Codes |
|---|----------------------|---|
| Inclusion Criteria | | |
| Hypertension: Defined as <ol style="list-style-type: none"> 1 hospital admission with a hypertension diagnosis 2. OHIP claim with hypertension diagnosis, followed within 2 years by either an OHIP claim or hospital admission with a hypertension diagnosis | CIHI-DAD OHIP | ICD-9: 401x, 402x, 403x, 404x, 405x ICD-10: I10, I11, I12, I13, I15 OHIP Dx: 401, 402, 403, 404, 405 |
| Exclusion Criteria | | |
| OHIP eligibility (continuously eligible with a 90-day grace period) Age less than 66 years old Ineligible for OHIP 1 year prior to index date Non-Ontario resident at index Missing Sex Death on or before index date | RPDB | N/A |
| Exposure | | |

| | | |
|------------------------------------|------------------|--|
| Sex | RPDB | |
| Outcomes | | |
| Coronary Artery Bypass Grafting | DAD-SDS, OHIP | <p>ICD 10: I099, I420, I425, I426, I427, I428, I429, I443, I500, I501, I509, I255, J81</p> <p>ICD 10 intervention code: 1HP53, 1HP55, 1HZ53GRFR, 1HZ53LAFR, 1HZ53SYFR</p> <p>OHIP fee code: R701, R702, Z429</p> <p>OHIP diagnosis code: 428</p> |
| Percutaneous Coronary Intervention | | <p>ICD-10: Z955</p> <p>CCI: 1IJ54GQAZ, 1IJ50</p> <p>OHIP fee: Z434, Z448, G298</p> |
| Myocardial Infarction | | <p>ICD-10: I21, I22</p> <p>ICD-10 intervention code: 1HP53, 1HP55, 1HZ53GRFR, 1HZ53LAFR, 1HZ53SYFR</p> |
| Congestive Heart Failure | | <p>Definition of ICES-derived CHF cohort: 1 Hospitalization or 1 OHIP/Emergency Department (ED) visit followed by 1 Hospitalization/ED visit/OHIP within one year.</p> |
| Ischemic Stroke | | <p>ICD-10: H341, I630, I631, I632, I633, I634, I635, I638, I639, I64</p> |
| Mortality and Cause of Death | ORGD | |
| Baseline Characteristics | | |
| Age, Income Quintile, Rurality | RPDB | |

| | | |
|-------------------------|---------|--|
| Coronary Artery Disease | DAD-SDS | ICD-10: I20, I21, I22, I23, I24, I25, Z955, Z958, Z959, R931, T822 |
| | OHIP | ICD-10 intervention code: 1IJ26, 1IJ27, 1IJ54, 1IJ57, 1IJ50, 1IJ76 OHIP fee code: R741, R742, R743, G298, E646, E651, E652, E654, E655, G262, Z434, Z448 OHIP diagnosis code: 410, 412, 413 |

| | | |
|---------------------------------|-----------------|--|
| Coronary Artery Bypass Grafting | DAD-SDS | ICD 10 : 1IJ76 |
| | OHIP | OHIP fee code: R742, R743, E654, E645, E652, E646 |
| Congestive Heart Failure | DAD-SDS OHIP | Definition of ICES-derived CHF cohort: 1 Hospitalization or 1 OHIP/Emergency Department (ED) visit followed by 1 Hospitalization/ED visit/OHIP within one year. |
| Myocardial Infarction | DAD-SDS | ICD 10: I21, I22 ICD 10 intervention code: 1HP53, 1HP55, 1HZ53GRFR, 1HZ53LAFR, 1HZ53SYFR |
| Ischemic Stroke | DAD-SDS | ICD 10: I62, I630, I631, I632, I633, I634, I635, I638, I639, I64, H341, I600, I601, I602, I603, I604, I605, I606, I607, I609, I61, G450, G451, G452, G453, G458, G459, H340 |
| Atrial Fibrillation | DAD-SDS | ICD 10: I48 |
| Arrhythmia | DAD-SDS | ICD 10: I48, I44, I45, I47, I4900, I4901, I491, I492, I493, I494, I498, I499, R000, R001 |
| | OHIP | OHIP fee code: G178, G179, G249, G261, G259, Z443, Z431, Z437 |
| Diabetes Mellitus | DAD-SDS | ICD 10: E10, E11, E12, E13, E14 |
| | OHIP | OHIP fee code: Q040, K029, K030, K045, K046 OHIP diagnosis code: 250 |

| | | |
|--|---------------------------|---|
| Dementia, Cognitive Impairment | CIHI- DEMENTIA | ICD-10: F00 - F03, F05, G30, G31, G31, G31, 90, G31 |
| Dialysis | CIHI-DAD OHIP | ICD-10: R849, R850, G323, G324, G325, G326, G330, G331, G332, G333, G860, G861, G862, G863, G864, G865, G866, G090, G091, G092, G096, G294, G294, G864, R850, Y84, H540, H740 CCI: PZ21HQBR, 1PZ21HPD4, 1PZ21 |
| Obesity | CIHI-DAD | ICD-10: E66 |
| Chronic Liver Disease | CIHI-DAD NACRS OHIP | ICD-10: 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, I864 I982 K711 K72 K77 Z944 OHIP FEE: Z551, Z554 OHIP DX : 571, 573, 070 |
| Chronic Obstructive Pulmonary Disorder | CIHI-DAD | ICD-10: J41, J43, J44 I278 I279 J40 J41 J42 J43 J44 J45 J46 J47 J60 J61 J62 J63 J64 J65 J66 J67 J684 J701 J703 |
| Chronic Renal Disease | CIHI-DAD | ICD-10: I12, I13 N03 to N07, N18-19, N25.0, Z490-492, Z940, Z992 |

| | | |
|--------------|-------------------|--|
| Major Cancer | CIHI-DAD OHIP | ICD10: 971, 980, 982, 984, 985, 986, 987, 988, 989, 990, 991, 993, C15, C18, C19, C20, C22, C25, C34, C50, C56, C61, C82, C83, C85, C91, C92, C93, C94, C95, D00, D05, D010, D011, D012, D022, D075 C81 C82 C83 C84 C85 C88 C96 C900 C902, C77 C78 C79 C80 Solid Tumor without Metastasis: C00 C01 C02 C03 C04 C05 C06 C07 C08 C09 C10 C11 C12 C13 C14 C15 C16 C17 C18 C19 C20 C21 C22 C23 C24 C25 C26 C30 C31 C32 C33 C34 C37 C38 C39 C40 C41 C43 C45 C46 C47 C48 C49 C50 C51 C52 C53 C54 C55 C56 C57 C58 C60 C61 C62 C63 C64 C65 C66 C67 C68 C69 C70 C71 C72 C73 C74 C75 C76 C97 OHIP: 203, 204, 205, 206, 207, 208, 150, 154, 155, 157, 162, 174, 175, 183, 185 |
| Seizure | CIHI-DAD NACRS | ICD10: G40, G41, R560, R568 |
| Osteoporosis | CIHI-DAD NACRS | ICD10: M80, M81, M82 |
| Medications | ODB | N/A |

Abbreviations: CCI, Canadian Classification of Interventions; CIHI-DAD, Canadian Institute for Health Information Discharge Abstract Database; ICD, International Classification of Diseases and Related Health Problems; NACRS, National Ambulatory Care Reporting System; ODB, Ontario Drug Benefit Claims; OHIP, Ontario Health Insurance Plan; RPDB, Registered Persons Database; ORGD, Office of the Registrar General-Deaths.

Supplemental Table S3: Antihypertensive medications identified for the study

ALPHA BLOCKERS

DOXAZOSIN MESYLATE
 PRAZOSIN
 TERAZOSIN

ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS

AMLODIPINE BESYLATE & PERINDOPRIL ARGININE SALT BENAZEPRIL
 BENAZEPRIL & HYDROCHLOROTHIAZIDE BENAZEPRIL CHLOROHYDRATE CAPTOPRIL
 CILAZAPRIL
 CILAZAPRIL & HYDROCHLOROTHIAZIDE ENALAPRIL MALEATE
 ENALAPRIL MALEATE & HYDROCHLOROTHIAZIDE ENALAPRIL SODIUM
 ENALAPRIL SODIUM & HYDROCHLOROTHIAZIDE ENALAPRILAT
 FELODIPINE & RAMIPRIL FOSINOPRIL
 FOSINOPRIL SODIUM HYDROCHLOROTHIAZIDE & LISINOPRIL HYDROCHLOROTHIAZIDE &
 QUINAPRIL HYDROCHLOROTHIAZIDE & RAMIPRIL
 INDAPAMIDE & PERINDOPRIL

TERT.BUTYLAMINE LISINOPRIL
PERINDOPRIL ARGININE
PERINDOPRIL ARGININE & INDAPAMIDE PERINDOPRIL ERBUMINE
PERINDOPRIL TERT.BUTYLAMINE QUINAPRIL
RAMIPRIL TRANDOLAPRIL
TRANDOLAPRIL & VERAPAMIL

ANGIOTENSIN RECEPTOR BLOCKERS

AMLODIPINE BESYLATE & TELMISARTAN CANDESARTAN CILEXETIL
CANDESARTAN CILEXETIL & HYDROCHLOROTHIAZIDE EPROSARTAN MESYLATE
EPROSARTAN MESYLATE & HYDROCHLOROTHIAZIDE
HYDROCHLOROTHIAZIDE & IRBESARTAN HYDROCHLOROTHIAZIDE
LOSARTAN POTASSIUM & HYDROCHLOROTHIAZIDE
OLMESARTAN MEDOXOMIL & HYDROCHLOROTHIAZIDE
QUINAPRIL HYDROCHLOROTHIAZIDE & TELMISARTAN HYDROCHLOROTHIAZIDE
VALSARTAN
IRBESARTAN
LOSARTAN POTASSIUM
OLMESARTAN MEDOXOMIL
TELMISARTAN

ANTIARRHYTHMICS

ADENOSINE
AMIODARONE
BRETILIUM TOSILATE DEXTROSE & LIDOCAINE DISOPYRAMIDE
DRONEDARONE FLECAINIDE
GLUCOSE & LIDOCAINE
IBUTILIDE FUMARATE & LIDOCAINE
LIDOCAINE & DEXTROSE
LIDOCAINE HYDROCHLORIDE & DEXTROSE MEXILETINE
PROCAINAMIDE PROPAFENONE QUINIDINE
QUINIDINE GLUCONATE
QUINIDINE POLYGALACTURONATE
QUINIDINE SULFATE
TOCAINIDE

BETA BLOCKERS

ACEBUTOLOL
ATENOLOL
ATENOLOL & CHLORTHALIDONE
BENDROFLUMETHIAZIDE & NADOLOL BETAXOLOL
BETAXOLOL & PILOCARPINE
BISOPROLOL FUMARATE
BRIMONIDINE TARTRATE & TIMOLOL MALEATE

BRINZOLAMIDE & TIMOLOL MALEATE
CARVEDILOL
ESMOLOL
FELODIPINE & METOPROLOL
HYDROCHLOROTHIAZIDE & METOPROLOL
HYDROCHLOROTHIAZIDE & PINDOLOL
HYDROCHLOROTHIAZIDE & PROPRANOLOL HCL
LABETALOL
LEVOBUNOLOL METOPROLOL
METOPROLOL SUCCINATE
METOPROLOL SULFATE
METOPROLOL TARTRATE
NADOLOL
OXPRENOLOL
PINDOLOL
PROPRANOLOL
SOTALOL
TIMOLOL
TIMOLOL MALEATE
TIMOLOL MALEATE & SODIUM CHLORIDE

CALCIUM CHANNEL BLOCKERS

ACETYLSALICYLIC ACID & NIFEDIPINE
AMLODIPINE BESYLATE
AMLODIPINE BESYLATE & ATORVASTATIN CALCIUM CLEVIDIPINE
DILTIAZEM
ERYTHRITYL TETRANITRATE
FELODIPINE
ISRADIPINE
NICARDIPINE
NIFEDIPINE
VERAPMIL

CLONIDINE

MEDICATIONS THAT INCLUDE SODIUM-GLUCOSE TRANSPORT PROTEIN 2 INHIBITORS

CANAGLIFLOZIN & METFORMIN
CHLORPROPAMIDE DAPAGLIFLOZIN
DAPAGLIFLOZIN & METFORMIN
EMPAGLIFLOZIN

LOOP DIURETICS

BUMETANIDE FUROSEMIDE

ETHACRYNIC ACID

NITRATES

NITRATE

GLUCOSE & NITROGLYCERINE

ISOSORBIDE DINITRATE I

SOSORBIDE-5-MONONITRATE

NITROGLYCERIN

THIAZIDE DIURETICS

CHLORTHALIDONE

HYDROCHLOROTHIAZIDE

HYDROCHLOROTHIAZIDE & TIMOLOL MALEATE

INDAPAMIDE

PERINDOPRIL & INDAPAMIDE

METOLAZONE

Supplemental Table S4. Unadjusted hazard ratios (HR) for MACE

| | HR (95% CI) |
|---------------------------------|--------------------|
| VARIABLE | |
| Sex (reference=male) | 0.76 (0.74, 0.77) |
| Rural residence (reference=no) | 0.87 (0.84, 0.89) |
| Age | 1.07 (1.07, 1.07) |
| Income quintile | |
| 0 | ref |
| 1 | 1.06 (1.02, 1.09) |
| 2 | 0.96 (0.93, 0.99) |
| 3 | 0.93 (0.90, 0.96) |
| 4 | 0.89 (0.86, 0.92) |
| COMORBIDITIES | |
| Coronary artery disease | 1.21 (1.17, 1.25) |
| Myocardial infarction | 1.15 (1.08, 1.22) |
| Coronary artery bypass grafting | 0.82 (0.72, 0.94) |
| Atrial fibrillation | 1.08 (0.98, 1.18) |

| | |
|---|----------------------|
| Arrhythmia | 1.13 (1.05, 1.22) |
| Ischemic stroke | 1.66 (1.53, 1.79) |
| Peripheral vascular disease | 1.37 (1.24, 1.50) |
| Diabetes | 1.34 (1.31, 1.37) |
| Chronic obstructive pulmonary disorder | 1.45 (1.38, 1.53) |
| Chronic liver disease | 0.98 (0.90, 1.08) |
| Cancer | 1.04 (1.00, 1.08) |
| Osteoporosis | 0.98 (0.82, 1.17) |
| Chronic renal disease | 1.22 (1.09, 1.35) |
| Congestive heart failure | 0.36 (0.33, 0.40) |
| ANTIHYPERTENSIVE MEDICATION USE AT INDEX DATE (REFERENCE=NO) | |
| Alpha-blocker | 1.09 (1.01, 1.18) |
| Angiotensin-converting enzyme (ACE) inhibitor | 1.04 (1.00, 1.08) |
| Antiarrhythmic | 1.21 (1.08, 1.35) |

| | |
|--|-------------------|
| Beta-blocker | 1.33 (1.28, 1.39) |
| Calcium channel blocker | 1.19 (1.14, 1.24) |
| Clonidine | 1.23 (0.92, 1.63) |
| Loop diuretic | 1.28 (1.21, 1.35) |
| Sodium-glucose transport (SGLT-2) inhibitors | 1.10 (0.90, 1.36) |
| Hydralazine | 1.25 (0.94, 1.67) |
| Thiazide diuretic | 1.14 (1.09, 1.19) |
| | |
| Number of antihypertensive medications | 1.00 (0.97, 1.03) |
| | |
| HEALTHCARE UTILIZATION | |
| Number of hospitalizations | 0.95 (0.93, 0.96) |
| Number of emergency room visits | 1.13 (1.11, 1.14) |
| Number of family physician visits | 1.00 (1.00, 1.00) |

SUPPLEMENTARY MATERIAL FOR CHAPTER 4

Supplemental Table S1. Checklist of recommendations for reporting of observational studies using the REporting of studies Conducting using Observational Routinely collected health Data (RECORD) Statement.

| | Item No. | STROBE items | Location in manuscript where items are reported (pages) | RECORD items | Location in manuscript where items are 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 | 1,3,4 | RECORD 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. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract. | 3,4 |
| Introduction | | | | | |
| Background rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 5 | | |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 5 | | |
| Methods | | | | | |
| Study Design | 4 | Present key elements of study design early in the paper | 6 | | |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 6 | | |
| Participants | 6 | (a) <i>Cohort study</i> - Give the | 6,7 | RECORD 6.1: The methods of study | 6,7,8,9 Figure 1 |

| | | | | | |
|------------------------------|---|---|-------|--|-----------------------|
| | | eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> - 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 <i>Cross-sectional study</i> - Give the eligibility criteria, and the sources and methods of selection of participants <i>(b) Cohort study</i> - For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> - For matched studies, give matching criteria and the number of controls per case | | population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 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. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage. | |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable. | 7,8 | RECORD 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. | Supplemental Material |
| 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 | 6,7,8 | | |

| | | | | | |
|------|---|---|---|--|--|
| Bias | 9 | Describe any efforts to address potential sources of bias | 7 | | |
|------|---|---|---|--|--|

| | | | | | |
|------------------------|----|---|----------|--|--|
| Study size | 10 | Explain how the study size was arrived at | Figure 1 | | |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why | 8,9 | | |
| Statistical methods | 12 | <p>(f) Describe all statistical methods, including those used to control for confounding</p> <p>(g) Describe any methods used to examine subgroups and interactions</p> <p>(h) Explain how missing data were addressed</p> <p>(i) <i>Cohort study</i> - If applicable, explain how loss to follow-up was addressed</p> <p><i>Case-control study</i> - If applicable, explain how matching of cases and controls was addressed</p> <p><i>Cross-sectional study</i> - If applicable, describe analytical methods taking account of sampling strategy</p> <p>(j) Describe any sensitivity analyses</p> | 8,9 | | |

| | | | | | |
|----------------------------------|--|----|--|---|-----------------|
| Data access and cleaning methods | | .. | | <p>RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.</p> <p>RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.</p> | 6,7 Figure 1 |
| Linkage | | .. | | RECORD 12.3: State whether the | 6,7 |

| | | | | | |
|--|--|--|--|---|--|
| | | | | <p>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.</p> | |
|--|--|--|--|---|--|

| | | | | | |
|----------------|----|---|--|---|----------|
| Results | | | | | |
| Participants | 13 | <p>(a) Report the numbers of individuals at each stage of the study (<i>e.g.</i>, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed)</p> <p>(b) Give reasons for non-participation at each stage.</p> <p>(c) Consider use of a flow diagram</p> | | <p>RECORD 13.1: Describe in detail the selection of the persons included in the study (<i>i.e.</i>, study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.</p> | Figure 1 |

| | | | | | |
|------------------|----|--|--|--|--|
| Descriptive data | 14 | <p>(a) Give characteristics of study participants (<i>e.g.</i>, demographic, clinical, social) and information on exposures and potential confounders</p> <p>(b) Indicate the number of participants with missing data for each variable of interest</p> <p>(c) <i>Cohort study</i> - summarise follow-up time (<i>e.g.</i>, average and total amount)</p> | | | 9 Table 1 |
| Outcome data | 15 | <p><i>Cohort study</i> - Report numbers of outcome events or summary measures over time</p> <p><i>Case-control study</i> - Report numbers in each exposure category, or summary measures of exposure</p> <p><i>Cross-sectional study</i> - Report numbers of outcome events or summary measures</p> | | | 10, 11, 12 Tables 2, 3; Figures 2, 3 |

| | | | | | |
|-------------------|----|--|--------|--|----------------------------------|
| Main results | 16 | (a) Give unadjusted estimates and, if applicable, confounder- adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | | | 10, 11 Tables 2,3 Figure 3 |
| Other analyses | 17 | Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses | | | 11, 12 |
| Discussion | | | | | |
| Key results | 18 | Summarise key results with reference to study objectives | | | 10, 11 |
| 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 | 11, 12 | RECORD 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. | 11, 12 |

| | | | | | |
|---|----|--|----------|--|----|
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 12,13,14 | | |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 14 | | |
| 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 | N/A | | |
| Accessibility of protocol, raw data, and programming code | | .. | 15 | RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code. | 15 |

| | | |
|--|------|--|
| | | |
| Exposure | | |
| Sex | RPDB | |
| Outcomes | | |
| Laboratory Investigations: | OLIS | |
| Urinalysis | | OLIS: 20454-5 |
| Sodium | | OLIS: 2951-2 |
| Potassium | | OLIS: 2823-3, 6298-4 |
| Serum creatinine | | OLIS: 14682-9 |
| Hemoglobin A1c | | OLIS: 4548-4, 17855-8, 17856-6, 41995-2, and 71875-9 |
| Fasting blood glucose | | OLIS: 14771-0 |
| Serum total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), non-HDL lipoprotein, triglycerides | | OLIS: 14646-4, 14647-2, 14927-8, 22748-8, 32309-7, 39469-2 |
| Standard 12-lead electrocardiogram | OHIP | G313, G310 |
| First medication(s) | ODB | 1. Beta blockers (S_BBL) |

| | | |
|---------------------------------|---------------------|--|
| prescribed for hypertension | | <ol style="list-style-type: none"> 2. Angiotensin-converting enzyme (ACE) inhibitors (S_ACE) 3. Angiotensin Receptor Blockers (ARBs) (S_ARB) 4. Thiazide Diuretics (S_THD) 5. Calcium Channel Blockers (CCB) (S_CCB) 6. Antiarrhythmics (BC_ANA) 7. Antihypertensives (S_BBL + S_ACE + S_ARB + S_THD + S_CCB) 8. Nitrates (BC_NIT) 9. Clonidine (BC_CLD) 10. Loop Diuretic (BC_DIC) 11. Alpha-blocker (BC_ALPH, S_TER, S_PRA, S_DOX) (S_AB) 12. Hydralazine (S_HYD) 13. Sodium-glucose transport inhibitors (SGLT_2) |
| Baseline Characteristics | | |
| Age, Income Quintile, Rurality | RPDB | |
| Coronary Artery Disease | DAD-SDS OHIP | <p>ICD-10: I20, I21, I22, I23, I24, I25, Z955, Z958, Z959, R931, T822</p> <p>ICD-10 intervention code: 1IJ26, 1IJ27, 1IJ54, 1IJ57, 1IJ50, 1IJ76</p> <p>OHIP fee code: R741, R742, R743, G298, E646, E651, E652, E654, E655, G262, Z434, Z448</p> <p>OHIP diagnosis code: 410, 412, 413</p> |

| | | |
|---------------------------------|---------|---|
| Coronary Artery Bypass Grafting | DAD-SDS | ICD 10 : 1IJ76 |
| | OHIP | OHIP fee code: R742, R743, E654, E645, E652, E646 |
| Congestive Heart Failure | DAD-SDS | Definition of ICES-derived CHF cohort: 1 Hospitalization or 1 OHIP/Emergency Department (ED) visit followed by 1 Hospitalization/ED visit/OHIP within one year. |
| | OHIP | |

| | | |
|--------------------------------|---------------------------|---|
| Myocardial Infarction | DAD-SDS | ICD 10: I21, I22 ICD 10 intervention code: 1HP53, 1HP55, 1HZ53GRFR, 1HZ53LAFR, 1HZ53SYFR |
| Ischemic Stroke | DAD-SDS | ICD 10: I62, I630, I631, I632, I633, I634, I635, I638, I639, I64, H341, I600, I601, I602, I603, I604, I605, I606, I607, I609, I61, G450, G451, G452, G453, G458, G459, H340 |
| Atrial Fibrillation | DAD-SDS | ICD 10: I48 |
| Arrhythmia | DAD-SDS OHIP | ICD 10: I48, I44, I45, I47, I4900, I4901, I491, I492, I493, I494, I498, I499, R000, R001 OHIP fee code: G178, G179, G249, G261, G259, Z443, Z431, Z437 |
| Diabetes Mellitus | DAD-SDS OHIP | ICD 10: E10, E11, E12, E13, E14 OHIP fee code: Q040, K029, K030, K045, K046 OHIP diagnosis code: 250 |
| Dementia, Cognitive Impairment | CIHI- DEMENTIA | ICD-10: F00 - F03, F05, G30, G31, G31, G31, 90, G31 |
| Dialysis | CIHI-DAD OHIP | ICD-10: R849, R850, G323, G324, G325, G326, G330, G331, G332, G333, G860, G861, G862, G863, G864, G865, G866, G090, G091, G092, G096, G294, G294, G864, R850, Y84, H540, H740 CCI: PZ21HQBR, 1PZ21HPD4, 1PZ21 |
| Obesity | CIHI-DAD | ICD-10: E66 |
| Chronic Liver Disease | CIHI-DAD NACRS OHIP | ICD-10: 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, I864 I982 K711 K72 K77 Z944 OHIP FEE: Z551, Z554 OHIP DX : 571, 573, 070 |

| | | |
|--|----------|---|
| Chronic Obstructive Pulmonary Disorder | CIHI-DAD | ICD-10: J41, J43, J44 I278 I279 J40 J41 J42 J43 J44 J45 J46 J47 J60 J61 J62 J63 J64 J65 J66 J67 J684 J701 J703 |
| Chronic Renal Disease | CIHI-DAD | ICD-10: I12, I13 N03 to N07, N18-19, N25.0, Z490-492, Z940, Z992 |

| | | |
|--------------|-------------------|--|
| Major Cancer | CIHI-DAD OHIP | ICD10: 971, 980, 982, 984, 985, 986, 987, 988, 989, 990, 991, 993, C15, C18, C19, C20, C22, C25, C34, C50, C56, C61, C82, C83, C85, C91, C92, C93, C94, C95, D00, D05, D010, D011, D012, D022, D075 C81 C82 C83 C84 C85 C88 C96 C900 C902, C77 C78 C79 C80 Solid Tumor without Metastasis: C00 C01 C02 C03 C04 C05 C06 C07 C08 C09 C10 C11 C12 C13 C14 C15 C16 C17 C18 C19 C20 C21 C22 C23 C24 C25 C26 C30 C31 C32 C33 C34 C37 C38 C39 C40 C41 C43 C45 C46 C47 C48 C49 C50 C51 C52 C53 C54 C55 C56 C57 C58 C60 C61 C62 C63 C64 C65 C66 C67 C68 C69 C70 C71 C72 C73 C74 C75 C76 C97 OHIP: 203, 204, 205, 206, 207, 208, 150, 154, 155, 157, 162, 174, 175, 183, 185 |
| Seizure | CIHI-DAD NACRS | ICD10: G40, G41, R560, R568 |
| Osteoporosis | CIHI-DAD NACRS | ICD10: M80, M81, M82 |
| Medications | ODB | N/A |

Abbreviations: CCI, Canadian Classification of Interventions; CIHI-DAD, Canadian Institute for Health Information Discharge Abstract Database; ICD, International Classification of Diseases and Related Health Problems; NACRS, National Ambulatory Care Reporting System; ODB, Ontario Drug Benefit Claims; OHIP, Ontario Health

Insurance Plan; OLIS, Ontario Laboratories Information System; RPDB, Registered Persons Database.

Supplemental Table S3: Antihypertensive medications identified for the study

ALPHA BLOCKERS

DOXAZOSIN MESYLATE
PRAZOSIN
TERAZOSIN

ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS

AMLODIPINE BESYLATE & PERINDOPRIL ARGININE SALT BENAZEPRIL
BENAZEPRIL & HYDROCHLOROTHIAZIDE BENAZEPRIL CHLOROHYDRATE CAPTOPRIL
CILAZAPRIL
CILAZAPRIL & HYDROCHLOROTHIAZIDE ENALAPRIL MALEATE
ENALAPRIL MALEATE & HYDROCHLOROTHIAZIDE ENALAPRIL SODIUM
ENALAPRIL SODIUM & HYDROCHLOROTHIAZIDE ENALAPRILAT
FELODIPINE & RAMIPRIL FOSINOPRIL
FOSINOPRIL SODIUM HYDROCHLOROTHIAZIDE & LISINOPRIL HYDROCHLOROTHIAZIDE & QUINAPRIL
HYDROCHLOROTHIAZIDE & RAMIPRIL
INDAPAMIDE & PERINDOPRIL
TERT.BUTYLAMINE LISINOPRIL
PERINDOPRIL ARGININE
PERINDOPRIL ARGININE & INDAPAMIDE PERINDOPRIL ERBUMINE
PERINDOPRIL TERT.BUTYLAMINE QUINAPRIL
RAMIPRIL TRANDOLAPRIL
TRANDOLAPRIL & VERAPAMIL

ANGIOTENSIN RECEPTOR BLOCKERS

AMLODIPINE BESYLATE & TELMISARTAN CANDESARTAN CILEXETIL
CANDESARTAN CILEXETIL & HYDROCHLOROTHIAZIDE EPROSARTAN MESYLATE
EPROSARTAN MESYLATE & HYDROCHLOROTHIAZIDE
HYDROCHLOROTHIAZIDE & IRBESARTAN HYDROCHLOROTHIAZIDE
LOSARTAN POTASSIUM & HYDROCHLOROTHIAZIDE
OLMESARTAN MEDOXOMIL & HYDROCHLOROTHIAZIDE
QUINAPRIL HYDROCHLOROTHIAZIDE & TELMISARTAN HYDROCHLOROTHIAZIDE
VALSARTAN
IRBESARTAN
LOSARTAN POTASSIUM
OLMESARTAN MEDOXOMIL
TELMISARTAN

ANTIARRHYTHMICS

ADENOSINE
AMIODARONE
BRETYLIUM TOSILATE DEXTROSE & LIDOCAINE DISOPYRAMIDE
DRONEDARONE FLECAINIDE
GLUCOSE & LIDOCAINE
IBUTILIDE FUMARATE & LIDOCAINE
LIDOCAINE & DEXTROSE
LIDOCAINE HYDROCHLORIDE & DEXTROSE MEXILETINE

PROCAINAMIDE PROPAPENONE QUINIDINE
QUINIDINE GLUCONATE
QUINIDINE POLYGALACTURONATE
QUINIDINE SULFATE
TOCAINIDE

BETA BLOCKERS

ACEBUTOLOL
ATENOLOL
ATENOLOL & CHLORTHALIDONE
BENDROFLUMETHIAZIDE & NADOLOL BETAXOLOL
BETAXOLOL & PILOCARPINE
BISOPROLOL FUMARATE
BRIMONIDINE TARTRATE & TIMOLOL MALEATE
BRINZOLAMIDE & TIMOLOL MALEATE
CARVEDILOL
ESMOLOL
FELODIPINE & METOPROLOL
HYDROCHLOROTHIAZIDE & METOPROLOL
HYDROCHLOROTHIAZIDE & PINDOLOL
HYDROCHLOROTHIAZIDE & PROPRANOLOL HCL
LABETALOL
LEVOBUNOLOL METOPROLOL
METOPROLOL SUCCINATE
METOPROLOL SULFATE
METOPROLOL TARTRATE
NADOLOL
OXPRENOLOL
PINDOLOL
PROPRANOLOL
SOTALOL
TIMOLOL
TIMOLOL MALEATE
TIMOLOL MALEATE & SODIUM CHLORIDE

CALCIUM CHANNEL BLOCKERS

ACETYLSALICYLIC ACID & NIFEDIPINE
AMLODIPINE BESYLATE
AMLODIPINE BESYLATE & ATORVASTATIN CALCIUM CLEVIDIPINE
DILTIAZEM
ERYTHRITYL TETRANITRATE
FELODIPINE
ISRADIPINE
NICARDIPINE
NIFEDIPINE
VERAPMIL

CLONIDINE

MEDICATIONS THAT INCLUDE SODIUM-GLUCOSE TRANSPORT PROTEIN 2 INHIBITORS

CANAGLIFLOZIN & METFORMIN
CHLORPROPAMIDE DAPAGLIFLOZIN
DAPAGLIFLOZIN & METFORMIN
EMPAGLIFLOZIN

LOOP DIURETICS

BUMETANIDE FUROSEMIDE
ETHACRYNIC ACID

NITRATES

NITRATE
GLUCOSE & NITROGLYCERINE
ISOSORBIDE DINITRATE I
SOSORBIDE-5-MONONITRATE
NITROGLYCERIN

THIAZIDE DIURETICS

CHLORTHALIDONE
HYDROCHLOROTHIAZIDE
HYDROCHLOROTHIAZIDE & TIMOLOL MALEATE
INDAPAMIDE
PERINDOPRIL & INDAPAMIDE
METOLAZONE

Supplemental Table S4. Recommended guideline recommended antihypertensive therapy.(16)

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|--|
| No comorbidity: any 1 or more of: |
| ACEi |
| ARB |
| Calcium channel blocker |
| Thiazide or thiazide-like diuretic |
| Beta blocker |
| |
| Diabetes: any 1 or more of: |
| ACEi |
| ARB |
| Calcium channel blocker |
| Thiazide or thiazide-like diuretic |
| |
| Congestive Heart Failure: any 1 or more of: |
| ACEi |
| ARB |
| Beta blocker |
| |
| Ischemic Stroke: any 1 or more of: |
| ACEi |
| Thiazide or thiazide-like diuretic |
| |
| Coronary Artery Disease: any 1 or more of: |
| ACEi |
| ARB |
| Calcium channel blocker |
| Beta blocker |