A NEW APPROACH TO ADDRESSING POLYPHARMACY IN OLDER CANADIANS: HYPERTENSION TREATMENT INTENSITY

by

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Abstract

This dissertation develops the concept of treatment intensity of asymptomatic conditions (such as hypertension) by examining the potential link between drug treatment for asymptomatic conditions and polypharmacy. Research addressing overtreatment has typically focused on reducing either the total number of medications or identification of potentially inappropriate medications. Multi-morbidity, including both symptomatic, e.g. arthritis, and asymptomatic conditions, e.g. hypertension, increases with age and may be an important driver of increased polypharmacy.

Hypothesis #1: There is an association between treatment intensity of hypertension and general polypharmacy. Treatment of hypertension has shown that it can reduce the risk of morbidity and mortality in studied populations. However, the evidence for benefit of treatment in people ≥70 years old has not been consistent. To explore how hypertension is treated and the possible relationship to polypharmacy, I designed two cross sectional studies: a cohort of 214 nursing home patients where I found that patients with treated systolic blood pressure (SBP) <128 mmHg had a RR 1.77 (1.07-2.96) of being prescribed ≥9 medications. And, a cohort of 25,737 community-dwelling people ≥70 years old, where I found treated SBP <120 or DBP <70 mmHg also had significant associations with increased prescribing.

Hypothesis # 2: Treatment of hypertension to SBP <120 mmHg is associated with increased harm, specifically, an increase in incident dementia. Some observational

studies have found an increased risk of dementia with lower SBP. I created a cox proportional hazards model to examine risk for incident dementia and associations with various treatment intensities of hypertension in a large cohort of Canadians and found a significant decreased risk of incident dementia for every 1 mmHg increase in SBP, HR 0.991 (95%CI 0.987-0.995, p = <.0001).

Conclusion: In the populations studied, increased treatment of hypertension is associated with increased polypharmacy and treatment of SBP to <120 mmHg is associated with an increased hazard ratio for incident dementia. Treatment intensity, and the use of upper and lower treatment thresholds, may aid future polypharmacy research and general clinical care of older Canadians.

Lay Summary

As people age they typically have more health conditions which can lead to the use of multiple medications. Some research has suggested that taking too many medications (polypharmacy) can increase the risk of side effects, costs and inconvenience. Some diagnoses are made based on biomedical measurements rather than specific symptoms a person feels. Hypertension is a common asymptomatic condition diagnosed using measurements, not symptoms. It's possible that asymptomatic conditions play a special role with polypharmacy. This research describes how hypertension is currently being treated in people ≥70 years old. We explore the possibility that hypertension treatment patterns, in both nursing homes and the community, are related to polypharmacy, and that too much hypertension treatment may increase specific harms, such as an earlier diagnosis of dementia. We propose that hypertension treatment should use a specific treatment range to reduce harms and polypharmacy.

Preface

This dissertation is based upon a program of work inspired by my clinical work as a family physician providing care in community and residential care facilities in Vancouver. I identified and designed the research program with guidance from my supervisor, Dr. Scott Garrison, and other members of my committee.

Chapters 1 and 2 describe the path of my work to get to this dissertation, and how it is set in the context of current literature regarding polypharmacy and overtreatment of older people. I argue for the need of a new approach to polypharmacy assessment with consideration of asymptomatic conditions and set up how high blood pressure will be used as the example as to how it may impact future research and clinical practice. I was responsible for all of this work.

Chapter 3 is an extended version of a published manuscript. This project received ethics approval from UBC Providence Research Ethics Board (certificate H14-00014) and Vancouver Coastal Health Research Institute (certificate V14-00014). Creation of the linked data set was organized by myself and data gathering from the paper charts was completed in 2013 by Ms. Charmaine Lam (medical student hired through the UBC Faculty of Medicine Summer Student Research Program). Paper chart referencing for frailty score calculation was completed by Dr. Kate Foulds and Dr. Brittany Rance, UBC family practice residents who completed this work as part of their academic requirements for residency) in November 2014. I was responsible for the project design,

all statistical analysis and writing of both the manuscript and this chapter. All authors listed were involved in reviewing the manuscript. Early versions of this work were also accepted, via peer review, for oral presentation at the Nov., 2015 Family Medicine Forum, Toronto and Oct., 2015 North American Primary Care Research Group Conference in Cancun, Mexico.

The studies presented in Chapters 4 and 5 were designed by myself with consultation regarding the statistical analysis plan from my committee members, Dr.'s Scott Garrison and James McCormack. Michael Law, Joel Singer, Ruth Lavergne and Lindsay Hedden also provided advice regarding the exact formatting of the logistic and cox regression models. The dataset was obtained from the Canadian Primary Care Sentinel Surveillance Network (CPCSSN). Ms. Sandra Peterson programmed and formatted the dataset into the variables needed for the proposed analysis. I wrote the statistics syntax and performed the analysis myself. These two studies are covered by an ethics approval from UBC Providence Research Ethics Board (certificate H15-02435). This work has not yet been presented nor published beyond this dissertation.

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List of Abbreviations

A1c	glycosylated hemoglobin
ADE	adverse drug event
ARR	absolute risk reduction
CPCSSN	Canadian Primary Care Sentinel Surveillance Network
CPG	clinical practice guideline
DBP	diastolic blood pressure
NNH	number needed to harm
NNT	number need to treat
OR	odds ratio
PIM	potentially inappropriate medication
RCT	randomized control trial
RR	relative risk
SBP	systolic blood pressure

Glossary

"Just Right" treatment – Symptoms of the treated condition and/or adverse effects of treatment are absent or manageable and/or surrogate measure is between targeted upper and lower threshold and both harms of disease and treatment are minimized, (and personal preferences are incorporated). See Section 1.7.

Overtreatment - Symptoms of the treated condition may be ameliorated but adverse effects of treatment are not tolerable and/or the surrogate measure is below lower threshold and/or the harms of treatment increased (could include personal preferences being ignored). See Section 1.7.

Polypharmacy - There is no single definition for polypharmacy, however, generally, most definitions presented in the literature refer to presence of excessive drug therapy that should be ameliorated by reduction of the numbers of drugs prescribed. See section 1.2.

Treatment intensity - the balance between amount of treatment (numbers and doses of drugs) and effects of the treatment (symptom/condition modification and adverse effects). See Section 1.12, 1.7 and Chapter 2.

Undertreatment – Symptoms of a treated condition persist to an unreasonable level or the targeted surrogate measure remains above the targeted upper threshold and/or

harms of disease increased (could also include personal preferences being ignored).

See Section 1.7.

Acknowledgements

I did this work on the unceded traditional territory of the xʷməθkwəy̓əm (Musqueam) Sḵwx̱wú7mesh (Squamish), and Səl̓ílwətaʔ (Tsleil-Waututh). Hay chxw q'a.

Thank you to my supervisors and committee, Dr.'s Scott Garrison, Sabrina Wong, James McCormack and Margaret McGregor. You generously offered advice when asked, guided when needed and supported the evolution of my dissertation from where it started to what is submitted here.

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Very special thanks to my family. My dear daughter, Norah Marie McCracken Sparks was 14 months old when I started this PhD. She has been both accepting of my work and not afraid to tell me what she needed. Her growth as a person has happened alongside this dissertation and I thank her for all the surprises and demands for my time. While those demands have extended my work schedule they have also have let me be a more balanced person, and most importantly, a mom (and, once this dissertation is accepted, I will make a real baby book, with photos of you, not tables and

figures). To my husband, Brett Sparks, for his unwavering emotional and financial support (and almost constant explaining to confused relatives about why I had chosen, once again, to go back to school). Thank you to the rest of my family, especially Aunt Beat who spoke kindly and babysat frequently and my Dad, for the unconditional love and reminders of my internal resources to get this work finished. Also, my sibs, Andru, for his effective brotherly torture methods when I wanted to walk away from it all, Mike and Pete for basic math refreshers and Colleen for her optimism.

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Dedication

To my mother, Mary McCracken (1946 -1987), who taught me to question everything and always speak for what is right. And to my daughter, Norah, to whom curiosity and bravery come so naturally.

Chapter 1: Introduction

1.1 Overview

The purpose of this dissertation is to explore the possible relationships between asymptomatic conditions, such as hypertension, and polypharmacy. This work may be useful in developing research and clinical strategies to reduce the ill-effects of polypharmacy. The following broad hypotheses were tested in three quantitative observational studies: There is an association between treatment intensity of hypertension and general polypharmacy (Chapters 3 and 4). Treatment of hypertension to lower levels of surrogates is associated with increased harm; specifically, a decrease in time to new diagnosis of dementia (Chapter 5).

The remainder of Chapter 1 provides rationale for the hypotheses examined, set out definitions of polypharmacy, frailty, dementia, and treatment intensity, and review the current literature in these areas. Chapter 2 will explain the rationale for choice of hypertension treatment as the sample condition with which to conduct this work.

1.2 Research Chronology

I began practicing as family doctor in July 2008 and built a practice where I saw patients in clinic, hospital, and nursing homes. Over the first few years, I had three experiences in my nursing home work where I saw an unexpected improvement in a patient's condition when medications were stopped. These three patients were older and frail,

and none had capacity to speak about their own experience due to the effects of dementia. Figure 1.1 provides a description of one of these experiences.

Mrs. B was a 75-year-old woman who lived in a well-regarded, publicly-funded nursing home for seven years. She had schizophrenia and as she aged, she developed aggressive behaviors and personal neglect requiring 24/7 nursing care. She had no living family members to support her. After five relatively stable years, her physical condition slowly deteriorated to the point where, essentially, she sat in her wheelchair or lay in her bed, looking out the window. She accepted food when offered but did not participate in any facility activities nor speak aloud.

Her schizophrenia was treated with atypical antipsychotics, as would be prescribed to a younger patient with similar illness. These agents had treated her reasonably well most of her life. She also took medications for hypertension, diabetes, high cholesterol, joint pain and osteoporosis. At her annual medication reviews her physician had simply renewed her 10 separate prescriptions (= to 18 pills/day) as previously prescribed because they "appeared to be working", and her treatment typically followed published clinical guidelines.

Mrs. B's course of illness changed with an episode of vomiting of blood (a sign of a potentially life-ending gastrointestinal bleed). Given her previously expressed wishes, level of frailty, and apparent advanced dementia, the health care team, which included an ethics advisor, decided to treat only her symptoms of pain and vomiting and not investigate the cause of her bleeding. Everyone expected that she would die within a week or two. The palliative plan meant stopping most of her regularly dosed medications, except for the ones for pain. To the surprise of the care team, within ten days, Mrs. B was sitting up in her bed on her own, smiling and saying good morning to the nursing staff. She even asked if she could go play bingo with her roommates in the dining hall. Some of her behavior symptoms returned and required small doses of the same atypical antipsychotics that she had previously received, but she lived a much more vibrant life for an additional 8 months.

(The patient name and some details of this story have been altered to protect the patient's identity, however, this is an actual clinical situation experienced by the author).

Figure 1.1 The story of Mrs. B

There was little in the published literature to explain what was happening and I began asking nursing home colleagues whether they had had similar experiences. Everyone I spoke to had at least one story of a “miraculous” patient response to discontinuation of medicines; however, there was no consensus for an approach that could reliably predict when this would happen.

As I studied this issue more, I came to understand that the ideas of a) possible harms from excessive drug prescription (polypharmacy) and b) treatment of the same by “deprescribing” had been around at least since William Osler famously said, “One of the first duties of the physician is to educate the masses not to take medicine.”[1] These concerns have reappeared in the medical literature since then,[2–5] however, the quality of studies has been mixed and clarity about how to transfer the concepts to regular clinical care remained almost absent.

The lack of population-specific research in this area seemed unjust to me and I wanted to learn how to generate evidence that could change practice and provide better care to older, frail people, especially those who also had dementia. Initially, I proposed a randomized controlled trial (RCT) of deprescribing for frail elders admitted to nursing homes. However, this project ended up being not feasible for my doctoral studies due to barriers to recruitment and resources available, as outlined in Appendix A. During the failed recruitment efforts, I had noted that a smaller-than-expected proportion of potential participants were taking more than five regular medications[6] (an RCT inclusion criteria) and almost everyone appeared to be treated for hypertension. I drew up a

proposal to do a cross-sectional study to see exactly what kind of prescribing was going on, with a special focus on blood pressure. I used the same six facilities and a randomization mechanism to select a sample of 220 participants. This work is presented in Chapter 3 and was key to informing the remainder of my doctoral investigation. From this dataset, we observed that 70% of the sample had a diagnosis of hypertension and 60% of the sample had a SBP <130 mmHg.[7]

1.1.1 Developing the specific questions for this dissertation

Could treatment of asymptomatic conditions be an important cause of polypharmacy? Considering what I had learned so far about polypharmacy and the effects of deprescribing, some new concepts began to emerge. An asymptomatic condition like hypertension was diagnosed in 70% of the nursing home patients studied, even though this population in BC has a life expectancy of only 24 months.[8] Few nursing home patients have the ability to verbalize treatment preferences or experiences of adverse effects such as low blood pressure, dry mouth, cough, lethargy, dizziness and headache. None of the clinical trials that inform our knowledge of harms and benefits of hypertension treatment have included people with this level of co-morbidity. Even if we assumed there may be some benefit from treatment, how could we tell if we were overtreating this asymptomatic condition? And what if overtreatment were a source of harm that could be negatively impacting people like Mrs. B.?

Discussions with my committee led me to realize that there was little published knowledge of how hypertension was actually being treated for people over the age of 70

in Canada (Chapter 4), and that clinicians did not have adequate data to provide reasonable estimates of the harms and benefits of that treatment to patients or to their proxy decision makers (Chapter 2 and 5). It appeared the research done on more well and/or younger people was being applied to this less well and older population and we weren't sure what effects this was having.

With these observations in hand, I began to wonder about the possible connections between asymptomatic chronic disease and polypharmacy and fortuitously was introduced to Dr. Sabrina Wong, who is the Network Director of BC Canadian Primary Care Sentinel Surveillance Network (CPCSSN) node. She had already worked with Dr. Garrison and was able to describe the exciting potential of CPCSSN (section 1.2.2) for research applications.[8] Dr. Wong agreed to join my committee to facilitate the transition of my program of research to its new focus.

In 2015, I developed a plan of study to expand my knowledge of overtreatment. I had previously wanted to assess an intervention to address too many medications (polypharmacy), and changed my focus to examining the amount of treatment for asymptomatic conditions, specifically, hypertension (hypertension) as a source of polypharmacy, and possibly harmful overtreatment. The goal being a fulsome exploration of the amount and types of medications used to treat hypertension and their effect on various blood pressure measures (e.g. SBP, DBP, pulse pressure).

1.2.1 Treatment intensity and hypertension

The combination of treatment choice, dose, and its effect is named *treatment intensity* for this dissertation. This concept is used to study treated hypertension and explore the potential utility of an upper treatment threshold (to start) and a lower threshold (to reduce or stop). These thresholds could then communicate more accurate estimates of harms and benefits of undertreatment, treatment and overtreatment to the patient or their proxy and enable true shared decision making. Treatment intensity does not have much presence nor an existing gold standard definition within medical literature. Section 1.6 and 1.7 will provide additional detail about how this concept will be used for this dissertation and Chapter Two provides a complete definition and rationale for the use of treatment intensity in this work.

In Mrs. B's case, a treatment intensity approach might have led me to identify possible overtreatment and taper medications until any symptoms re-emerged. Perhaps discontinuing them altogether if the symptoms were not observed, given her high level of co-morbidity and previously expressed wishes for minimal intervention. She might have had more time feeling well. Certainly, her story and those of my colleagues' patients, continued to inspire me to find some way to systematically explore these possible effects.

1.2.2 Identifying an accessible study population

CPCSSN is a network of networks across Canada, where primary care clinicians voluntarily participate in electronic medical record extraction of de-identified data for the

purposes of chronic disease surveillance, quality improvement, and approved research purposes. It is an actively growing database of clinical data on primary care activities for over 1 million Canadians who receive care from more than one thousand participating family physicians and nurse practitioners (sentinels).[8]

The CPCSSN database was able to provide a very large cohort, more than 200,000 people ≥70 years old, whose detailed medical records enabled my exploration of treatment intensity for community-dwelling people in primary care (at this time, CPCSSN does not include nursing home patients). With a sample this size we could make a robust description of how hypertension is being treated along with concurrent "other prescribing" (Chapter 4). The size and length of the cohort also lent themselves well to using a Cox proportional hazards model to measure the associations between treatment intensity of hypertension and serious risks, such as a new diagnosis of dementia (Chapter 5). In 2016, I wrote the research protocols, gained data access permissions and a new ethics application, and found appropriate mentorship to learn the statistical methods needed for the planned analysis. Since January 2017, I have been working on this dissertation.

The remainder of Chapter One outlines key concepts in this body of work, including: polypharmacy, the role of aging, frailty and dementia in drug treatment and section 1.9 will introduce how treatment intensity could function as a novel marker for polypharmacy.

1.2 Polypharmacy, defined

With her ten daily prescriptions and potentially avoidable excessive sedation, there is no doubt that Mrs. B (Figure 1.1) suffered ill-effects from what is known as polypharmacy. The umbrella term “polypharmacy” captures an evolving field of study marked by concern over the possible harms of excessive prescribed medication.[7] Polypharmacy has been found to be a risk factor for higher mortality and morbidity, particularly for those who are very old and/or frail. However, it is unclear whether polypharmacy itself poses a risk to patients or whether it serves as a marker for patients with more comorbidity.[9,10] There is little data available about the pharmacokinetics and dynamics of most pharmaceuticals in older people, because the majority of commonly prescribed medications have not been studied in older people.[11,12] The existing literature suggests that increased toxicity and unwanted adverse effects likely occur at higher rates[13,14] due to alterations in diffusion, distribution and excretion.[15] Similarly, drug-drug interactions are possibly more frequent and severe,[6,16,17] but at this time we know little about how and why certain types, numbers, or combinations of drugs may be harmful in older people.

There is no single definition for polypharmacy, nor a guide for which conditions or for which specific populations the many definitions should apply. However, there are two broad categories into which most current research falls: 1) those that count drugs, and 2) those that name certain drug classes as “potentially inappropriate.” Counting drugs results in the identification of a specific range or number of drugs that is considered polypharmacy. Reducing the number of drugs is the desired outcome. “Potentially

Inappropriate Medications" (PIM's) are identified on lists and have been theorized, or are actually known, to increase adverse effects for older people. Discontinuing the PIMs is the desired outcome.

1.2.1 Identifying drugs to count

In order to count drugs, we must first identify what we are counting. This includes: where the list of medicines comes from (e.g. administrative data set, patient self-report, primary care health record, etc) and which substances will be counted.[18–20] The time period over which the counting is done should be clear. Ideally, the dose, route of administration, frequency, and duration should be specified. Whether the substance requires a prescription or not will also influence what the final count will be. Figure 1.3 summarizes the information elements that should be considered for accurate counting of drugs. To date, there is no gold standard by which to define how medications are counted, nor which specific number can be used to diagnose polypharmacy. Details of how counting is done is not always clearly stated in published research findings and one review reported as many as 138 definitions of polypharmacy being used in the literature.[21] Currently a systematic review of definitions is underway.[22] The experiments presented in this dissertation will clearly identify the number of drugs defined to be polypharmacy, and how they were counted. Section 1.4 will discuss prevalence of various definitions of polypharmacy.

1. **SOURCE OF DRUG LIST** - Specify source of drug list(s) (e.g. patient self report, governmental database or primary care electronic medical record)
2. **TIME PERIOD FOR DRUG COUNTING** - State time period over which prescription information is included (e.g. single day or 365 day period) is collected.
3. **PRESCRIBED, DISPENSED or CONSUMED** – Specify if it is drugs prescribed, dispensed or drugs consumed that is being counted, detail how method used is confirmed.
4. **PRESCRIPTION DETAILS** - Identify how each of the following will be counted/reported:
    a. ROUTE OF ADMINISTRATION – Will all routes of administration be counted? (e.g. topical, IV, IM, SC, PV, PR all included, or only PO)
    b. DIFFERENTIATION OF SIZE OF DOSE - Specify if size and frequency of dose of a particular chemical entity will be differentiated, (e.g. will 300 mg of quetiapine BID be counted the same way as 6.25 mg TID), or if there be reporting of e.g. variance from WHO's defined daily dose (DDD).
    c. REGULAR versus PRO RE NATA (PRN) - If "prn" prescriptions are included, clarify if the prescription is counted when a prescription is present or only included if medication is actually dispensed/consumed (describe how this information is obtained).
    d. PRESCRIPTION DURATION - prescription durations (e.g. if short course of corticosteroids or antibiotics would be included or only those prescribed more than once for 30 days or longer).
5. **MULTIPLE PRESCRIPTIONS FOR SAME MEDICATION** - Explain how multiple listings of same chemical compound will be handled.
    a. SAME DAY DOSING - For same drug, different dose amounts on same day (e.g. If quetiapine is prescribed as 6.25mg qam and 100 mg qhs, will this be counted as as one or two medications for the total count).
    b. DIFFERENT FORMULATION - For e.g. long acting and short acting of same compound, are they one drug or two? Use of WHO ATC codes may be useful here.
6. **MULTIPLE PRESCRIPTIONS FOR SAME DRUG CLASS** – particularly relevant if counting over a time period longer than one month, if e.g. two drugs from same class are present in total time period, but follow each other sequentially, as might be the case if switching from a name brand to a generic equivalent, will this count as one or two drugs? Use of WHO ATC codes may be useful here.
7. **OVER THE COUNTER ITEMS and VITAMINS/MINERALS** - Specify if a prescription is needed for the item to be included, and if so, as per what region's prescription formulary, and/or if over the counter items such as vitamin D, acetaminophen, potassium, lactulose, sennosides, etc will also be counted.

Figure 1.2 Information elements needed to accurately count drugs

1.2.2 Lists of Potentially Inappropriate Medications (PIMs)

Multiple approaches exist for the identification of PIMs. These approaches are based on the theoretical discussions of how aging likely affects pharmacokinetics and dynamics or prescribed medications.[13] Drugs tolerated in someone younger or more well may have negative effects in someone older or less well. Lists of PIMs were designed to

prevent adverse drug reactions that may occur more frequently in an older person. The majority of methods (list-based tools) were developed using a modified Delphi method[23,24] and typically include a definition of the age group to which they apply. The Beers criteria, often recognized as the first of these methods, was published in 1991[25] and has been revised many times by the American Geriatrics Society.[26] The various lists contain similar drug classes and have the highest concern raised for those drugs with the most anticholinergic effects.[23]

Additionally, the modified Delphi process has been used to identify potentially inappropriate drug lists that apply to people with advanced dementia. This work builds on the Beers list by including medications which may be of questionable benefit, rather than having a risk of causing an adverse effect, due to the patient's prognosis.[27–29] A 2016 systematic review by Todd et al.[30] looked specifically at inappropriate prescribing of preventative medication for patients with "life-limiting illness" (defined variably by the 19 studies included). This review noted most of the existing tools to assess medication appropriateness do not include a way to address prevention medications. Prevalence of PIMs has also been well established[28,31] and reviews of the efficacy of these methods and their ability to reduce harm for patients,[23,32] these results will be reviewed in section 1.5. As an example of the limitation of current methods, Mrs. B would not have had any medications removed with the use of the 2015 Beers list. Even her atypical antipsychotic would be considered appropriate because she had a primary diagnosis of schizophrenia.

1.3 Prevalence of polypharmacy

We do not have an exact definition of what number of drugs equals polypharmacy however, we do have some indications that medication use is increasing. In Canada, a 2014 report of nursing home residents found that two-thirds of residents were taking more than 10 medications.[6] An Irish study found that between 1997 and 2012, the number of community-dwelling people ≥65 years old taking five or more medications had increased from 17.8% to 60.4%, and those taking 10 or more medications had increased from 1.5% to 21.9%.[33] Studies based elsewhere have also found trends towards increasing numbers of prescriptions over time.[19,34,35]

The literature remains divided over whether a higher number of drugs is itself a problem. Concerns of possible under-prescribing in older people[36] have also been described.[37,38] However, there appears to be emerging agreement there is a problem with people taking medications that are not needed or unintentionally harmful.[39,40]

1.4 Harms associated with polypharmacy

The data regarding harms associated with polypharmacy come almost exclusively from observational studies.[10,41–43] An adverse drug event can be hard to define, variable in intensity, and may not be recorded in regular clinical records.[44] Information from people presenting to emergency departments has provided a significant source of information about what is known regarding adverse drug events (ADEs). ADEs requiring an emergency department visit or hospitalization are better documented. A 2003 study of older community-dwelling people found that 27.6% of 1,523 adverse drug events

presenting to the emergency room were likely avoidable at the time of prescribing.[45] A 2016 analysis of emergency visits caused by adverse drug events identified that causative agents were rarely those that are included on the lists of “inappropriate” medications.[46]

A 2014 systematic review of 50 studies found mixed results about the specific relationships between polypharmacy and unwanted outcomes.[42] However, studies which adjusted for co-morbidity generally found an association between higher numbers of medications and falls, fall outcomes, adverse drug events, hospitalization, mortality, measures of personal function, and cognition. The authors raised important concerns regarding the mixed results and heterogeneity of methods and, like many writers in this field, called for robustly designed prospective trials from which more definitive results might be obtained.

While the literature is unable to provide exact estimates of harms from too much medication, neither can it accurately estimate any benefits from polypharmacy. Within the emerging field of investigation of effects of “larger” or “inappropriate” amounts or types of medication, there is a general consensus that more exact and reliable information is needed to design future studies and guide shared decision making about clinical treatments.

1.3 Efficacy of interventions to address polypharmacy

There has been an almost fourfold increase in the number of new polypharmacy papers indexed in PubMed in the last ten years (from 220 in 2006 to 839 in 2016).[47] However, there is no conclusive evidence about the best way to respond to polypharmacy. A typical polypharmacy intervention has a medication review, using a standardized tool or approach, performed by a pharmacist, physician or multidisciplinary team. The medication review counts medications and looks for potentially inappropriate drugs or drugs of questionable benefit, that could be discontinued based on published lists of concerning drugs, for example the Beers criteria[26] or STOPP/START.[48] Outcome measures usually include the numbers of medications prescribed, hospitalizations, mortality and occasionally, falls, quality of life and adverse drug events.

There are multiple systematic reviews of these published interventions designed to reduce/address polypharmacy and their effect on patient outcomes. Some reviews focus only on patients who are community dwelling[9,32,49,50] or who reside in nursing homes[51,52] and/or those with frailty[53] or advanced dementia.[54] While the exact question addressed for each of these reviews varies slightly, they all mention the lack of clear findings, heterogeneity of study designs and the need for more definitive research. The patients studied in this work have complex health conditions and are often affected by multiple illnesses. In addition, some of the conditions (e.g. dementia) reduce their ability to provide direct report of their health status. Recruitment to studies is usually difficult and inadequate sample sizes[55] or use of convenience samples[56] may further complicate the ability to have reproducible results.

1.4 Multi-morbidity and asymptomatic chronic conditions

Mrs. B had active psychiatric (schizophrenia) and joint disease (osteoarthritis), diagnoses which affected her ability to function independently and for which drugs were prescribed to reduce symptom burden. She had also accumulated a list of asymptomatic risk factor conditions that were being treated, including hypertension, diabetes and osteoporosis. Increases in the number of concurrent diagnoses experienced by a patient (multimorbidity) with aging has been well-described.[57] Each new diagnosis can be treated using a disease-specific clinical practice guideline, with drug therapies, which naturally increases numbers of drugs prescribed.[58–60]

Treatment of symptomatic conditions can be guided by monitoring of symptoms, even if a patient is non-verbal, observations about her/his comfort and function provide valuable information about a drug's efficacy. In contrast, asymptomatic diseases rely on surrogate markers and risk estimates. Treatment of these conditions does not relieve e.g. pain or agitation, but rather modifies risks of theoretically unwanted sequelae, such as stroke, fracture or death. The calculations of risk reduction are made on more well and younger research participants.[11,61] Few people who look like Mrs. B are included in randomized controlled trials, so results are difficult to generalize to patients like her. Section 2.1 will compare efficacy measures for symptomatic versus asymptomatic conditions. Sections 1.7.3 and 1.7.4 will review how natural death and patient treatment goals further complicate treatment of asymptomatic conditions.

1.5 Aging, frailty, dementia and shared decision making

Advancing age has been found to be a significant factor in adverse drug reactions.[62–64] However, there are no consensus definitions in the medical literature of what age constitutes “old” or “elderly”. For the purposes of this thesis, older adults will be defined as being ≥ 70 years old. Some observational studies of polypharmacy prevalence have found increasing age to be associated with increased numbers of prescriptions.[65]

An increase in the proportion of the population that is elderly is a global phenomenon, but is most prevalent in more developed countries.[66] There is debate internationally and in Canada about what impact, in terms of costs and health services utilization patterns, the increasing numbers of older people will have on the health system.[67,68] However, it is reasonable to assume that with more older people, there would be an increase in the number of people affected by polypharmacy, which would then add both costs[69,70] and the numbers experiencing potential harms from excessive prescribing.

Frailty

Frailty lacks a consensus definition, yet is widely recognized as a medical syndrome negatively affecting function and prognosis of older adults.[71–73] Most descriptions of frailty refer to a loss of mental and physical resources that exceeds what would normally be expected due to age.[72] Older adults who are also frail have been found to have higher rates of negative health outcomes; such as mortality, hospitalization, and reduced independence.[74] Multiple frailty indexes, or tools to diagnose frailty, have

evolved and are used to describe prevalence, explain differences in outcomes and be used as outcome measures themselves in intervention studies.[71]

Polypharmacy is associated with increased risk of developing frailty[10] as well as being a risk factor for increased harm from medications.[75] Frailty instruments rely on either a description of a person's phenotype, or summation of her/his acquired deficits that produce a score or grade that corresponds to a level of fitness or frailty.[76] While each tool has specific features, some work has been done to compare outcomes for tools which has shown reasonable congruence.[77,78] For this dissertation, use of the descriptor frail will refer to a person or population who has met, or is presumed to have met, the minimum score or level to be defined as frail, for whichever tool was used.

Dementia

Dementia is another condition that is of special relevance to older adults. While its medical description is more definitive, its symptoms present along a wide and related disability that complicates its utility in clinical practice.[79] The incidence of dementia increases with age[80] and the increased demand on health care requirements, as the disease progresses, are a concern for many health systems.[81] Effect on quality of life, personal relationships, and functional independence can be severe. Current treatments for dementia are limited and do not provide any disease reversing component.[82] The disease process often reduces a patient's ability to voice their preferences, wishes, and physical reactions to drugs, either positive or negative. Some work has begun to explore whether dementia may have specific associations with adverse drug effects.[14] Co-

morbidity and dementia are common[83] and it follows that so is polypharmacy.[84] For this dissertation, use of the term dementia will refer to those people who have been identified as meeting diagnostic criteria or are being prescribed a medication whose sole indication is for dementia.

Inevitability of death

Modern medical treatments, including drug therapy, have conferred some undeniable benefits; however, infinite deferral of death is not one of them.[85] As one disease is "cured" another will take its place as a rising cause of death. Common sense may indicate that, unless faced by a sudden, unexpected death, there be some relevant point at which medical intervention and pharmacological therapy shifts from a curative approach to the offering of treatments intended to alleviate unwanted suffering. However, definition of this point, as well as lack of clear evidence to guide the changes to treatment alternatives, is lacking.

The manner of one's dying, while possibly front of mind for a patient, is not typically part of a treatment plan for an older person.[86] In medicine culture, the general assumption can be that all morbidity should be prevented if we have tools to allow us to do so. Biomedical research generally has had a single disease perspective rather than a whole life view, and avoidance of death from the disease under investigation is a win. This has resulted in multiple treatment algorithms for single diseases being applied to a single person, as discussed in section 1.6. The medications add up, and the possible causes of death are theoretically reduced,[85] but the inevitably of death is not.

Dementia stands out in this process, given that we lack a cure and the symptoms are so profoundly disabling. Associations between specific drug prescribing and changes to incident dementia have been described;[87–89] however, there are no clear conclusions about specific agents, dose, exposure length or predisposing factors. Mrs. B's cognitive and behavioral decline may have been affected by the drugs prescribed to her, but at the time I lacked both the awareness and evidence to attempt to address it. Having clear, population-specific estimates of increased or decreased risks of certain drugs and incident dementia would be of immediate and widespread interest.

Polypharmacy for people with dementia is a special problem where voicing symptoms, such as pain that could be ameliorated with pharmacological treatment, might be impaired by the disease's effects and therefore distressing symptoms could go untreated. Conversely, prior to having her/his insight affected by dementia, a patient may state they do not wish to die from the disease and would prefer the opportunity to die from e.g., a heart attack. However, their active neurological disease prevents them from saying so and a well-intentioned physician who treats their asymptomatic conditions with drugs may reduce their opportunity for such a death. Being able to provide patients and their families reasonable estimates of harms and benefits of specific treatments, and their combinations, would help move the "manner of dying" component into the light.[90] An informed choice that declined prescriptions to reduce cardiovascular risk factors may naturally address unwanted or unintentionally harmful polypharmacy.

Shared Decision Making

The historical perspective of “doctor knows best” has evolved to include informed consent and patient autonomy as more appropriate drivers for medical decision making. Research in this area is often focused on the specific topic of “shared decision making” and has seen a growing call for attention,[91] where reasonable estimate of harms and benefits of specific treatments may be conveyed to a patient and they can be guided, using their own priorities and values, to make a well-informed decision about which treatment they prefer and how much treatment is best for them. Concurrent research has shown that patient and provider preferences are often discordant.[92] A recently updated systematic review showed that using decision aids with patients often resulted in more conservative treatment choices.[93]

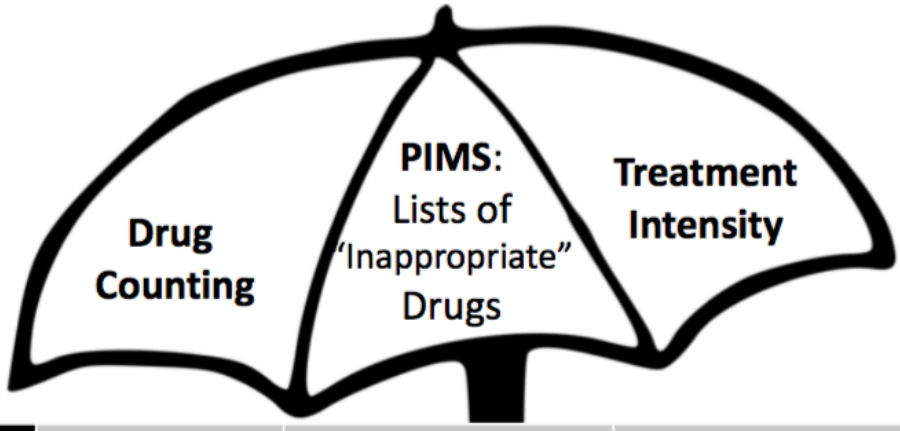
Processes to use shared decision making regarding polypharmacy have only begun to be studied and are not well-established.[94] Effective shared decision making for older people regarding combining and adding medications to a treatment plan requires reasonable estimates for effects (positive and negative) of particular drugs and combinations of drugs that can be used for the design of appropriate decision aids. These estimates of effects are currently quite limited. For patients like Mrs. B, it is hard to imagine how she could have been included meaningfully, but perhaps having an evidence-based expectation to try and include her might have presented the idea of decreasing some of her medications.

1.6 Treatment intensity and overtreatment reduction

There is ambiguity about the cause, accurate diagnosis and effective treatment of polypharmacy. The ambiguity also extends to being able to describe the “right amount” of medication for each individual. Yet the compelling story of patients like Mrs. B also shows the need for clarity and evidence. Frailty, dementia, natural death and shared-decision-making add to the complexity of designing rigorous research to evaluate possible solutions. Our existing methods of counting or identifying inappropriate drugs do not have a mechanism to address the particularly opaque role of prescribing for asymptomatic conditions in addressing polypharmacy.

The “right amount” of medication for each person would: treat troublesome symptoms, maximize function, be consistent with personal values and neither hasten nor prolong natural death. This is a tall order and perhaps not surprising that there is no clear answer in the literature about how to accomplish it in real life. However, it seems that the present polypharmacy approaches, using drug counting or avoidance of “inappropriate” medications, are limited. This dissertation introduces the concept of **treatment intensity**, and applied asymptomatic conditions give a new lens to observe polypharmacy and overtreatment. Treatment intensity permits a more nuanced way to define under, “just right” and overtreatment. Figure 1.4 shows the proposed link between this new concept of treatment intensity and the traditional

representations of polypharmacy as drug counting or identifying potentially inappropriate medications (PIMs).



UNDER treated	n/a	n/a	Symptoms remain OR SM above threshold
"just right"	LESS than threshold # of drugs	None of "inappropriate" drugs	Symptoms controlled & AE's minimized OR SM between upper & lower threshold
OVER treated	MORE than threshold # drugs	Any inappropriate drugs	AE's > desired OR SM below threshold

SM= surrogate marker, e.g. systolic blood pressure
AE = Adverse Effect, e.g. dizziness or falls

Figure 1.3 Treatment intensity definition as a new component in the description of polypharmacy

1.7 Definition of treatment intensity

Treatment intensity is defined as the balance between amount of treatment (numbers and doses of drugs) and effects of the treatment (symptom/condition modification and

adverse effects). Treatment intensity does not have a consensus-based definition in the published medical literature and has received very little explicit study. It is being explored in this dissertation as a way to understand excessive medical treatment of asymptomatic conditions.

To facilitate discussion of the measure, I introduce three categories: under treatment, "just right" treatment, and overtreatment, which may be useful for research to inform clinical decision making. The following examples illustrate how these concepts could be applied. Chapter 2 provides a complete explanation of how treatment intensity is applied to hypertension.

Example, symptomatic condition

For medication used for diffuse back pain, undertreatment would have the patient experiencing pain at levels that negatively affected mood and/or function. Overtreatment would result in e.g., excessive drowsiness that negatively affected function. "Just right" would provide maximal pain relief with minimal adverse effects.

Example, asymptomatic condition

Asymptomatic conditions are typically "silent" to the patient and picked up by measuring surrogate measures. For example, if an otherwise well 71 year old woman was found to have systolic blood pressure (SBP) e.g. ≥180mmHg on two or more measures, current guidelines[95] would recommend treatment to reduce risk for unwanted sequelae such as stroke and premature death. The 2017 Canadian Clinical Practice Guideline (CPG)

suggests that her blood pressure should be treated to SBP <140 mmHg. Failure to reach that target would designate her as “undertreated”. The CPG provides specific instructions about how to augment therapy with additional medications and/or higher dosing, so that the targeted SBP can be reached. Conversely, there is no mention in the CPG of what specifically would constitute overtreatment. The CPG does not provide a mechanism nor data source with which to quantify possible benefits and harms of the recommended treatments for a particular individual. Similarly, there is no discussion about how patient preference might modify treatment. An ideal definition of overtreatment of hypertension would: suggest appropriate monitoring for symptoms of adverse effects, e.g. increased falls, dry mouth or cognitive changes, clarify when possible harms of treatment exceed possible benefits, and how to consider patient preference (e.g., if this patient wishes to avoid death by cancer or dementia, and would welcome a natural death by myocardial infarction, it may be most appropriate to not treat her blood pressure).

The current evidence base for hypertension treatment lacks information to allow for such a robust definition of overtreatment, which may help explain why such guidance is missing from CPG’s. Without an ability to define overtreatment, “just right” treatment is also difficult to specify for an individual. Current practice is to presume that anyone whose SBP is below the targeted level, is receiving the correct amount of treatment.

Table 1.1 summarizes the proposed treatment intensity categories and the differences between symptomatic and asymptomatic measures.

Table 1.1 Definition of treatment intensity for symptomatic versus asymptomatic disease

	SYMPTOMATIC DISEASE e.g. joint pain	ASYMPTOMATIC CHRONIC DISEASE e.g. hypertension	
		Observed	***Patient Experience***
Undertreatment	Symptoms persist	Surrogate measure ABOVE upper threshold	Harms of <u>disease</u> increased
"Just right" treatment	Symptoms treated & adverse effects of treatment absent or manageable	Surrogate measure BETWEEN upper and lower threshold	Both harms of disease & treatment are minimized, (& personal preferences are incorporated)
Overtreatment	Symptoms treated but adverse effects of treatment not tolerable	Surrogate measure BELOW lower threshold	Harms of <u>treatment</u> increased (could include personal preferences being ignored)

1.4.1 Gaps in current research

Hypertension lends itself well to exploring the potential relationship between treatment intensity and polypharmacy given its prevalence, consistent reductions in absolute risks for studied populations, ubiquitous clinical practice guidelines, and regularly collected surrogates. However, the research in this field is nascent. Some work has described

prevalence where early findings suggest that aggressive treatment of hypertension in older people is not uncommon.[96] Very little research to date has examined precisely how hypertension is treated in Canada (including the type and number of agents) and to what effect (level of surrogate measure and patient-relevant harms and benefits) in people ≥70 years old. Therefore, a critical gap is an accurate description of how blood pressure changes with hypertension treatment, for people older than 70.

Once the prevalence of treated blood pressures has been described***, identifying a possible relationship between treated levels of SBP and general polypharmacy*** will inform whether efforts to address polypharmacy might usefully include de-intensification of treatment for specific asymptomatic chronic disease (e.g. hypertension). Defining the extent of such a relationship could help explain both the rising numbers of prescriptions being given to older people worldwide and why many existing polypharmacy interventions fail to be reproducible and consistent.

Experiments that ***define possible harms and benefits of various treatment intensities*** will ultimately be needed to justify future interventions that would attempt to intensify or de-intensify chronic disease treatment for older people. To date, there has been very little study of the effects of de-intensification of treatment for asymptomatic conditions.[96–98]

1.5 Overview of dissertation structure

The following is a brief overview of how each subsequent chapter relates to the exploration of the relationships between asymptomatic conditions, such as hypertension (hypertension) and polypharmacy, in the context of treatment intensity.

Chapter 2 more completely **defines treatment intensity** and provide a rationale for the use of hypertension as a model condition.

Chapters 3 and 4 present two cross sectional studies that make observations of how hypertension is treated in nursing home (Chapter 3) and community-dwelling (Chapter 4) older people and **associations between treatment intensity of hypertension and general polypharmacy**.

Chapter 5 presents a cohort study that uses a Cox proportional hazards model to **estimate harms associated with treatment of hypertension to specific SBP surrogate measures**, specifically, the relationship to incident dementia diagnosis.

Chapter 6 **summarizes the main findings** and present ideas of how they may be used in developing future research and clinical strategies to reduce the ill-effects of polypharmacy.

1.6 Data sources and ethics approval

The quantitative studies presented in Chapters 3, 4 and 5 draw on data from two sources: an original linked, cross-sectional dataset (WiseMed) and a pan-Canadian electronic medical record primary care data set from the Canadian Primary Care Sentinel Surveillance Network (CPCSSN). Two separate certificates of ethics approval were obtained from the Providence Health Care / University of British Columbia Research Ethics Board (H14-00014 and H15-02435). All observations, opinions and conclusions described in this dissertation are those of the author and do not reflect any opinions or policies of CPCSSN, nor Providence Health Care.

Chapter 2: Treatment intensity and hypertension

2.1 Overview

Chapter Two expands on the concept of treatment intensity introduced in Chapter One and explains why the study of hypertension in older people could help develop a more functional way to identify overtreatment and its potential harms. The public is routinely exposed to information about the need to diagnose and treat hypertension. A 2015 New York Times article referred to hypertension as a "silent killer",[99] a deadly asymptomatic condition that can shorten lives unnecessarily, while explaining the SPRINT trial.[100]

The SPRINT Trial compared two treatment thresholds, SBP of <140mmHg versus <120 mmHg, and was stopped early due to the "potential to save lives".[101] Large randomized control trials, such as SPRINT, have shown statistically significant benefits in treating hypertension to reduce outcomes for trial participants, such as cardiovascular, cerebrovascular, and mortality events. In light of this evidence, it may seem unusual—even dangerous—to suggest that treating hypertension could be part of the problem of overtreatment. This chapter explains why such an exploration is needed by way of a discussion of condition prevalence, current treatment patterns, availability of data, limitations of experimental studies, and contradictory observational data.

2.2 Hypertension prevalence and diagnosis

High blood pressure rarely has noticeable symptoms; however, research has shown that hypertension is a risk factor for cardiovascular morbidity and mortality.[102–104] Reporting of prevalence of a symptom-less risk factor requires the use of a surrogate measure feasibly collected for screening in primary care. Diagnosis of hypertension is made using a measure of blood pressure that exceeds a specific upper threshold. Drug treatments, to reduce the increased risks of unwanted sequelae (e.g. heart attack, stroke or death), rely on repeat measures of this surrogate to assess the level of response to therapy. Treatment of the surrogate below a certain threshold is theorized to reduce the unwanted sequelae. There is global interest in estimating prevalence of hypertension as an aid to designing public health interventions to reduce treatable mortality and morbidity.[105,106]

Current estimates of hypertension prevalence come from population data sources and are typically reported as four categories: prevalence, diagnosed, treated, uncontrolled.[107] A pre-specified single threshold of systolic blood pressure (SBP) is used for diagnosis and as a binary indicator of controlled or uncontrolled hypertension. For example, if the diagnosis threshold is defined as 140 mmHg, anyone in the population found with a SBP of >140mmHg is diagnosed as having hypertension and being uncontrolled. Use of one or more antihypertensive medications (data linkage to prescribing records or patient self-report) is used as an indicator of treatment, so a patient taking 2 antihypertensive medications and having a SBP of <140 mmHg would be treated and controlled.

2.2.1 Specific population estimates of prevalence

In 2015, Godwin et al. used a large sample of electronic medical records in primary care, from the CPCSSN database, to estimate prevalence of systolic blood pressure ≥140mmHg to be as high as 70% in Canadians ≥70 years old.[108] This was similar to the estimates made by Robitaille et al. in 2012, 62.6%-74.6% for ages ≥70 years old using the Canadian Chronic Disease Surveillance System.[109] In the US, a 2014 report from the National Health and Nutrition Examination Survey (NHANES) found that in a sample of 10,190 people ≥60 years old diagnosed with hypertension, 53% had an SBP ≤140 mmHg (78% of whom were taking antihypertensive medication).[110]

A UK study that included 144,403 patients ≥80 years old followed by family practices from 2001-2014 (Clinical Practice Research Datalink (CPRD)) found 53.1% had a systolic blood pressure ≥140 mmHg, 63% of whom were prescribed antihypertensive medications.[111] This study also applied a Frailty Index[112] and found that only 23% of those with moderate or severe frailty had SBP ≥140 mmHg. A 2017 study from Korea used a sample of 4352 community-dwelling adults ≥65 years old found that 62% were "hypertensive" (defined as a blood pressure ≥140 mmHg).[113] This study also designed and applied a frailty index, and in contrast to the Ravindrarajah et al.[111] study and found that frail elders had higher rates of hypertension (67.8% versus 49.2% for robust patients, $p<0.001$) and were more likely to receive an antihypertensive medication (number not specified), but less likely to achieve a treatment goal of 150 mmHg ($P=0.005$).

2.2.2 Problems with prevalence estimates

The studies above provide prevalence estimates between 53%[110] and 74.6%[109] and use heterogeneous methods to measure and report their findings. This includes variation in instruments used to measure blood pressure, number of measures included per person and reliability of linked data regarding whether people are receiving antihypertensive medications. It is physiologically normal for blood pressure to fluctuate. Hypertension Canada has defined the gold standard for accurate measurement of blood pressure to be a 24-hour ambulatory test,[114] which is an uncommon clinical method and unlikely to be the usual source of recorded blood pressure measures in databases used for prevalence estimates. This calls into question the accuracy of measures that are used to make the estimate of the prevalence of the condition.

The current prevalence reporting strategy, i.e. formatting into categories of prevalence, diagnosed, treated, and uncontrolled[105] reduces patients to a single surrogate measure. It does not acknowledge the potential for shared decision making where a patient is given the information about harms and benefits of treatment, as would apply to her as a unique individual and decides that s/he doesn't wish to treat her blood pressure below a particular threshold.

Despite these limitations, the existing evidence suggests there are large numbers of people ≥ 70 years old whose SBP is ≥140 mmHg and may be receiving treatment to reduce that surrogate measure. With such a large proportion of the population taking or

potentially being targeted to take antihypertensive medication, it is reasonable to examine possible connections between polypharmacy and harms of overtreatment.

2.3 The harms of hypertension, observational data

A population cohort study of more than a million people living in the UK by Rapsomaniki et al.[115] found that morbidity associated with blood pressure varied with age. Most harms became less frequent with categories of higher systolic blood pressures as age increased and almost all cardiovascular outcome harm ratios for those ≥80 years old had confidence intervals that included 1.00. In 2002, the Prospective Studies Collaboration found a more consistent increase in vascular mortality with both increasing SBP and DBP for all age groups but the analysis excluded anyone with previously diagnosed vascular disease. This study also described a less extreme proportional difference in vascular mortality for those older (80-89 years old) versus younger (40-49 years old).[104] Both of these large cohort studies found lower risk estimates as age increased.

2.4 Existing evidence for benefits of hypertension treatment

The possible prevalence of SBP ≥140 mmHg in more than half of people ≥ 70 years old, as described in section 2.2, and the increase in morbidity and mortality with increased SBP explains the drive to study of effects of treating blood pressure. There are two types of research that have been designed to assess this. Comparison of single or multiple antihypertensive drugs to placebo and comparison of a lower and higher specific SBP target measure achieved using one or more antihypertensive medications.

2.4.1 The benefits of hypertension treatment, randomized control trials

Treatment versus placebo

Trials examining benefits of treatment of hypertension began in the 1970's. A 2009 Cochrane review[116] collated data from all published trials that compared antihypertensive drug treatment to placebo (or no treatment) in people ≥60 years old. This review included 15 randomized control trials with 24,055 people with mean baseline SBP of 172 mmHg for isolated systolic hypertension trials and 182mmHg for all other trials. The intervention drug treatment was a thiazide(-like) diuretic in 11/15 of these studies and had various other agents for secondary treatment. The other four trials used methyldopa, a calcium channel blocker or a beta blocker as a first line agent. Table 2.1 summarizes the results of the Cochrane review by Musini et al. and presents the calculated absolute risk reduction and NNT for each finding. The authors also examined the reported rates of withdrawal from trial due to adverse events, rate for treatment group = 10.3%, rate for control group = 6.5%. Information regarding withdrawals was not consistently reported and these calculations only include 6914 of the total 24,055 trial participants. This Cochrane review provides a comprehensive description of the statistically significant benefits of treating systolic blood pressure ≥ 160 mmHg in people ≥ 60 years old.

Table 2.1 Summary of calculated absolute risk reduction and number needed to treat for multiple outcomes in published hypertension trials

		Relative Risk (95% confidence interval)	ARR - Absolute Risk Reduction (%)	NNT – Number Needed to Treat
Total Mortality	>60 years old over 4.5 years	0.90 (0.84-0.97)	0.014 (1.4%)	71
	>80 years old over 2.2 years	0.98 (0.87-1.10)	n/a	n/a
Cardiovascular Mortality	>60 years old	0.77 (0.68-0.86)	0.013 (1.3%)	76
	>80 years old	0.98 (0.81-1.19)	n/a	n/a
Non-cardiovascular Mortality	>60 years old	1.02 (0.92-1.14)	n/a	n/a
	>80 years old	-	-	-
Cerebrovascular Mortality	>60 years old	0.66 (0.53-0.82)	0.007 (0.7%)	142
	>80 years old	0.80 (0.58,1.11)	n/a	n/a
Coronary heart disease mortality	>60 years old	0.77 (0.65-0.90)	0.008 (0.8%)	125
	>80 years old	0.98 (0.69-1.40)	n/a	n/a
Cardiovascular Mortality and Morbidity	>60 years old	0.72 (0.68-0.77)	0.039 (3.9%)	25
	>80 years old	0.75 (0.65-0.87)	0.032 (3.2%)	31
Cerebrovascular Mortality and Morbidity	>60 years old	0.66 (0.58-0.74)	0.020 (2.0%)	50
	>80 years old	0.66 (0.52-0.83)	0.018 (1.8%)	56

Relative Risk (95% CI) from select figures in Musini, et al. 2009 Cochrane Review [116]
Absolute Risk Reduction (ARR) = Control rate - Intervention rate, from data in forest plots, only calculated for P values <0.05
Number Need to Treat = 1/ARR, only calculated for P values <0.05

A 2010 metanalysis by Bejan-Anjoulvant, et al[117] specifically examined heterogeneity of hypertension trial results for available data on patients >80 years old and using linear

meta-regression explored the relationship between intensity of treatment and blood pressure reduction and their effect on mortality. Their results suggested that when mortality reductions were achieved, it was in the trials with the least blood pressure reduction and fewest medications prescribed, and the therefore the lowest intensity of therapy. However, these results do not seem to have been recognized nor incorporated into more recent trial protocol designs, such as SPRINT.[118]

Treatment to a higher versus lower blood pressure target.

A newer trial design compares lower versus higher treatment goals. Two systematic reviews published in 2017, by Weiss et al.[119] and Garrison et al.,[120] provide summary evidence from applicable trials including people ≥ 60 years old. The Weiss review included 6 RCT's to assess benefits and harms of trials that compared lower and higher blood pressure treatment targets. They calculated RR for death, stroke and cardiac events using data from 41,491 patients and their analytic approach named the lower blood pressure to be the treatment and higher BP as the control in calculation of relative risk for treatment benefit:

- Mortality, RR 0.86 (95% CI 0.69-1.06)
- Stroke, RR 0.79 (95% CI 0.59-0.99)
- Cardiac events, RR 0.82 (95% CI 0.64-1.00)
- Withdrawals due to serious events RR 1.25 (95% CI 0.94-1.67)

The trials were judged to have a low risk of bias and the analyses had measures of heterogeneity between 13.3% and 16.2%. However, they deemed their findings of low

strength due to inconsistent results between trials and confidence intervals wide enough to vacillate between marked benefit and no effect.

Garrison et al.'s Cochrane review included 3 trials comparing specific SBP treatment targets of <150-160/95-100 mmHg versus <140/90 mmHg (higher versus lower) and compared risk of a higher blood pressure versus lower blood pressure (i.e. inverse of the Weiss approach) and found:

- Mortality, RR 1.24 (95% CI 0.99-1.54)
- Stroke, RR 1.25 (95% CI 0.94-1.67)
- Cardiac events, RR 1.19 (95% CI 0.98-1.45)
- Withdrawals due to serious events, RR 0.83 (95%CI 0.58-1.19)

This review found rates of heterogeneity to be 59%-79% and concluded the quality of evidence for all estimates was low. The conclusions of the systematic reviews were guarded about the possible additional benefit and harms that a lower target may bring to a person ≥ 60 years old.

Table 2.2 Comparison between two recent systematic reviews of mortality, stroke and cardiac events and trial withdrawals for adults ≥60 years old in hypertension treatment target trials

	Weiss et al., 2017[119] **Benefit of treatment to lower target**	Garrison et al., 2017[120] **Harm of higher systolic blood pressure**
Trials included in review	ACCORD, 2010 Cardio-Sis, 2009 HOT, 1998 SPRINT, 2015 JATOS, 2008 VALISH, 2010	VALISH, 2010 Wei, 2013 JATOS, 2008
Mortality	RR 0.90 (95% CI 0.83-0.98)	RR 1.24 (95% CI 0.99-1.54)
Stroke	RR 0.79 (95% CI 0.59-0.99)	RR 1.25 (95% CI 0.94-1.67)
Cardiac events	RR 0.82 (95% CI 0.64-1.00)	RR 1.19 (95% CI 0.98-1.45)
Withdrawals due to serious events	RR 1.25 (95% CI 0.94-1.67)	RR 0.83 (95%CI 0.58-1.19)

2.5 Limitations of current evidence

The randomized controlled trial and systematic review results presented above reflect the highest quality of evidence available to inform clinical practice. However, this evidence has limitations when applied to the idea of overtreatment.[121] Recalling Mrs. B from Chapter One, those patients who are older, frail, have dementia, and/or are experiencing multi-morbidity are not usually included in RCTs. The lack of representation in research studies, as well as some aspects of study design (e.g. choice

of outcome measures) and reporting (e.g. variable quality of data regarding adverse events), may limit the utility of applying these results to older people in general.[122,123]

2.5.1 Exclusion criteria

Both types of hypertension trials (i.e. those comparing any treatment to placebo and those comparing more and less intense blood pressure treatment goals) have comprehensive exclusion criteria. Table 2.3 summarizes the exclusion criteria for 5 commonly referenced hypertension trials that compare treatment intensities. Single disease clinical trials, by design, rarely include older adults, or those who are unwell, particularly those frail or demented.[62,125-127] Without adequate representation in the trials, this means that research results from the more well, and often younger, populations are applied to older people where the results may not be consistent with what was found in the trials.[11,12,127]

Table 2.3 Participant exclusion criteria for hypertension trials that compare treatment targets

	Frailty or dementia	Diabetes	Chronic kidney disease	CHF	Other reasons for exclusions
FEVER[128]	Unclear if excluded, but required a "willingness to cooperate"	Included, unless "un-controlled"	Excluded if creatinine >177 umol/l, or Men GFR < 32 Women GFR <24	Not specified	Cardiomyopathy, CVA or MI in last 6 months, unstable angina, gout, "serious" pulmonary or hepatic disease
JATO[129]	Excluded if "considered unsuitable as subjects"	Excluded if A1c >8%	Excluded if creatinine > 133 umol/l, or Men GFR <44 Women GFR <33	Excluded if NYHA II or higher	MI/angioplasty in last 6 months, atrial fibrillation, hypertensive retinopathy, AST or ALT >2x upper limit of normal, malignancy, collagen disease
SPRINT[101]	Excluded for dementia, or if living in nursing home, or if factors present that are "judged likely to limit adherence to interventions"	Excluded	Excluded if GFR <20	Any symptomatic HF within 6 months or EF <35%	History of CVA, or medical condition "likely to limit survival to less than 3 years" or any cancer diagnosed or treated in prior 2 years that is likely to limit trial completion.
VALISH[130]	Excluded if judged "to be inappropriate" by investigator	Included	Excluded if creatinine >177 umol/l, or Men GFR <32 Women GFR <24	Excluded if NYHA III or higher	CVA or MI in last 6 months, angioplasty within 6 months or planned, atrial fibrillation or flutter, "severe" aortic stenosis or other valvular disease or "serious" liver dysfunction
Wei, et al.[131]	Excluded if diagnosis of Alzheimer's disease	Included	Excluded if creatinine >265 umol/l, or Men GFR <20 Women GFR <15	Excluded if NYHA III or higher or if EF<40%	Valvular heart disease, CVA or MI in last 6 months, hepatic dysfunction, autoimmune disorders, malignant tumors, other "non-cardiovascular diseases potentially causing death before the end of the study."

Adapted, with authors' permission, from supplemental material of Weiss et al.[120]

Possible harm from applying trial results too broadly: the RALES study

The RALES study[132] provides an example of this disconnect and the real harms that may result. RALES was a heart failure RCT that found adding spironolactone to usual treatment reduced death by 30% and lowered hospital admission by 35% and found only "minor" incidence of hyperkalemia.[132] These landmark trial findings were observed to change clinical practice of heart failure prescribing in Ontario, Canada.[133] In 2004, Juurlink et al. showed that increasing rates of spironolactone prescription after RALES (34/1000 in 1994 to 149/1000 in 2001) were actually associated with increased rates of hospitalization for hyperkalemia (2.4 per 1000 patients in 1994 to 11.0 per 1000 patients in 2001 ($P<0.001$)) and mortality (0.3 per 1000 to 2.0 per 1000 patients ($P<0.001$)).[133] The expected benefit reported in RALES was not seen and in fact, signals of increased harm were observed. Juurlink et al. suggested that the "real life" finding of increased harm may be due to the application of trial findings to people who would not have been included in the trial.

Hypertension trials exclude many categories of people who routinely receive hypertension treatment in the community. It is possible that application of the findings from the trials outlined in section 2.3 may have unintended effects that were not found with the trial participants.

2.5.2 Trial design

Many of the pivotal hypertension treatment trials mentioned above used a composite end point of cardiovascular events, including death. The use of composite endpoints is common in cardiovascular research[134] and usually include 3 to 4 individual end points that vary in clinical significance. Previous analyses have noted discrepancies between the total number of individual events in a trial and those reported for composite outcomes. A composite outcome aids a researcher by increasing the number of events observed during an experiment, but may distort the overall estimate of effect as it could be applied to individuals. Some work has been done to understand the potential disconnect between what a trial finds as "significant result" and what is most meaningful to patients. There appears to be potential for difference between what is most important to the patient and measures of effect across all the included components. Importantly, treatment effects for a less patient-relevant component may result in misleading impressions of the impact of treatment.[135]

When we consider that at least some of the patients treated for hypertension will be naturally close to death, what they value as a treatment outcome should be considered when offering treatment choices. For an older person with multiple co-morbidities, avoidance of death might not be seen as the most important treatment outcome. As discussed in Section 1.7, they could prefer an increase in function or quality of life, or even being spared pill burden as a goal of treatment.[136] The use of composite endpoints makes communication of relevant harms and benefits more difficult for shared decision making in clinical settings.

2.5.3 Unpublished data

In their systematic review, Su Golder and colleagues[137] study the completeness of adverse event reporting, mainly associated with pharmaceutical interventions, in published articles as compared with other information sources. They concluded: “that much of the information on adverse events remains unpublished and that the number and range of adverse events is higher in unpublished than in published versions of the same study”. For example, in 11 studies that compared the numbers of adverse events in studies where matching of published and unpublished data was possible, 43-100% (median 63%) of adverse events were not reported in the published findings. While this work by Golder et al. was not limited to cardiovascular research, there is some indication that hypertension research may have similar issues. A review of 41 hypertension trials found that only 41% of published results papers[138] adhered to the ten recommendations of harms reporting outlined by CONSORT.[139] These reports raise concern regarding the validity of the study results, especially as a tool to estimate possible harms of treatments.

The combined issues of exclusion criteria, trial design, and possible underreporting of adverse events in published studies raises concerns about reliance on RCTs to inform treatment of hypertension in older people.[140,141] The next section will explain how this reliance is compounded when these trials are used for clinical practice guidelines.

2.6 Clinical practice guidelines and expert consensus

Hypertension clinical practice guidelines (CPG's) provide a "treatment road map" for primary care clinicians. CPG's identify thresholds at which treatments should be initiated or intensified based on existing research. Where specific trial evidence is not available, expert consensus is often used to provide specific advice for treatment,[142] usually by disease-specific specialists.[143] These CPG's are intended to collate and simplify the best available evidence to allow for more consistent treatment in primary care and, theoretically, reduce disease burden in populations overall.

A common criticism of CPGs is that they are usually single-disease focused and often recommend multiple medications to achieve guideline targets for a single surrogate measure, e.g. SBP. Someone having multiple diagnoses of chronic conditions, for example, hypertension, diabetes, osteoporosis and dyslipidemia may easily accrue multiple long-term medications.[59,96] Concern about use of these CPGs in older, more frail people has previously been raised.[144–146] CPGs do not routinely mention their potential limitations regarding older, frailer people. A 2015 systematic review of 47 CPG's for cardiovascular disease prevention found that only 49% of the CPG's mentioned benefits for older people and only 38% mentioned possible harms of following the guidelines.[144] The lack of representation of people with multi-morbidity, frailty and dementia in trials is a possible explanation for the occasionally divergent or converse outcome associations seen in observational research of this population.

2.6.1 Diagnosis, treatment, control definitions

High blood pressure CPG's rely on blood pressure measures to identify specific thresholds at which the potential benefit of the treatments theoretically exceeds the potential harms. They also include cues for when treatment should be intensified with a dose increase or addition of a new medication. These thresholds are used to indicate "success" of treatment, where blood pressure is "controlled," and conversely being in excess of the threshold is labelled "uncontrolled".[37,147]

Current CPG's rarely mention at which point (i.e. lower threshold) treatment should be stopped or reduced. Some CPG's provide a comment that "clinical judgment" should be used to determine at which point treatment is no longer beneficial.[144,145] According to the current Canadian Hypertension treatment guidelines, once a diagnosis of hypertension is made in any non-diabetic person, at any age or level of frailty[96] a systolic blood pressure below 140 mmHg is considered "controlled" and if above that is "uncontrolled". The Canadian guideline includes the following sentence, "Practitioners are advised to consider patient preferences, values, and clinical factors when determining how to best apply these guidelines at the bedside,"[96] but no additional information about how this might be done is provided, nor is any additional reference to patient preference or shared decision making made. Figure 2.1 shows the current Canadian Hypertension Education Program (CHEP) guideline threshold for controlled (<140 mmHg) and uncontrolled SBP (≥140 mmHg)[96] that is in wide use across the country.

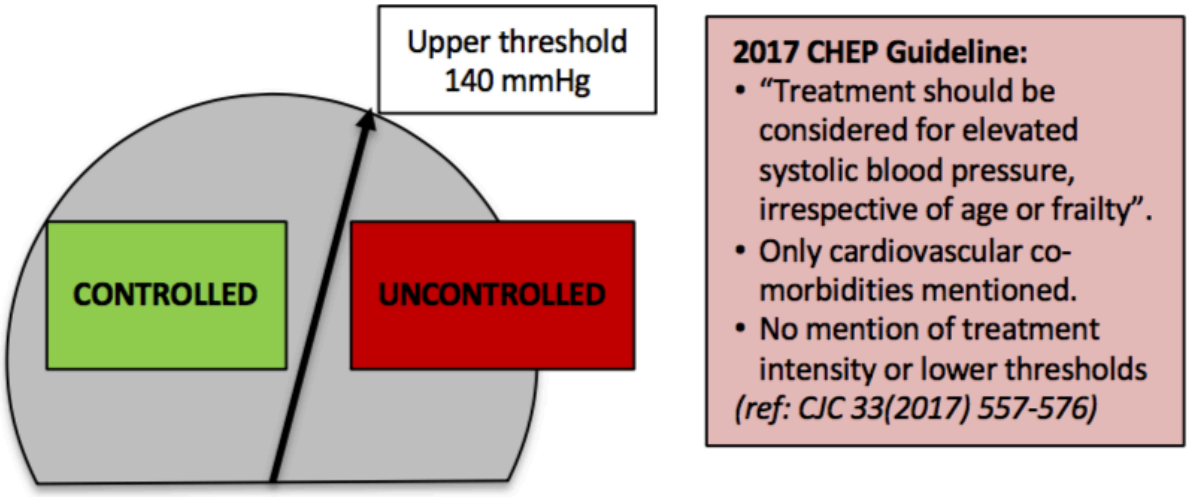


Figure 2.1 2017 Canadian Hypertension Education Program (CHEP) treatment threshold recommendations for people ≥70 years old

2.6.2 Guideline modification for older, frailer people

A recent review of hypertension guidelines for older people by Parekh et al.[148] compared four international guidelines published between 2011 and 2014, Figure 2.2 provides a visual comparison of the guideline recommendations.[149–152] The authors of this review also note that in 2016, the European Society for Hypertension and the European Union Geriatric Medicine Group published a joint statement saying that if treated blood pressure falls below 130 mmHg, treatment should be reduced or stopped.[153] This is the only lower threshold that was found in the published literature.

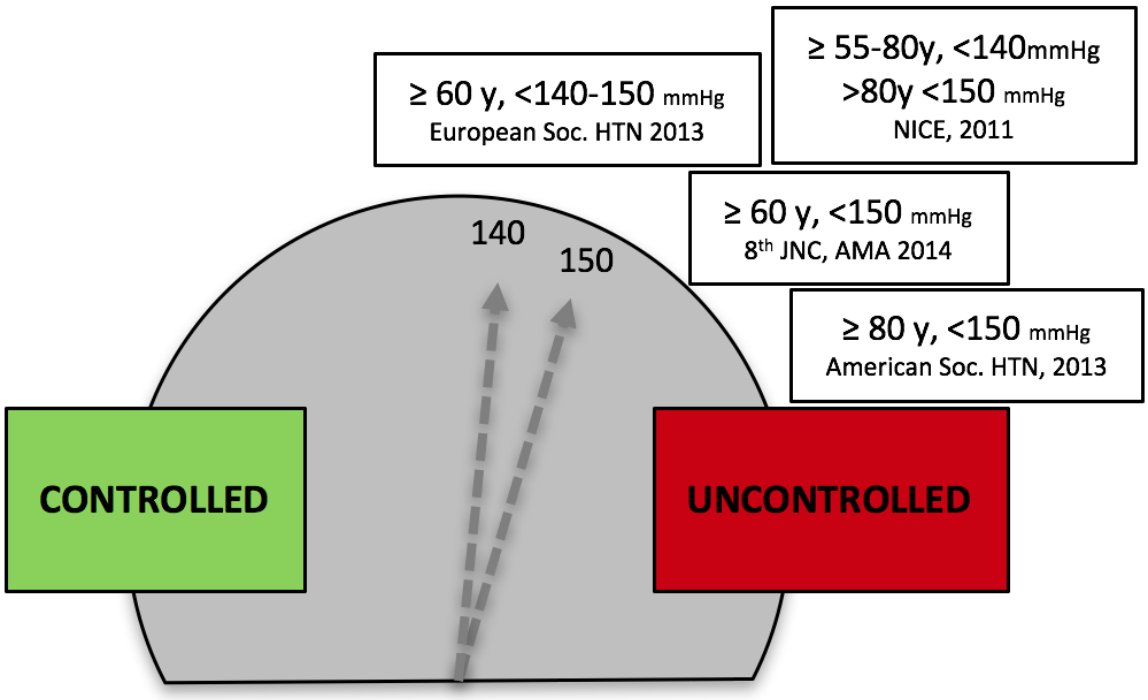


Figure 2.2 Comparison of treatment targets for 4 international hypertension guidelines

2.6.3 Reasonableness of clinical practice guideline systolic blood pressure thresholds

The use of a single SBP upper threshold as definition of controlled and uncontrolled is widely used in epidemiological research[108,154,155] as was presented in section 2.6. However, there is conflicting evidence as to whether treating below the thresholds outside of trials is even a reasonable goal.[156] An Australian trial of people aged 65-84 comparing the efficacy of ACE-I versus diuretic based drug regimens and using a 'Target BP' definition of a reduction of systolic/diastolic BP of at least 20/10 mm Hg and

BP <160/90 mm, found that only 50% could meet it after 60 months of follow up and that there was no difference in reaching that goal between the treatment groups.[157]

The majority of current CPG's for hypertension do not identify a lower threshold at which harms of treatment are likely to outweigh benefits. Figure 2.3 provides an example of how a more nuanced use of a treatment intensity approach to hypertension CPG's would possibly identify both over and under treatment.

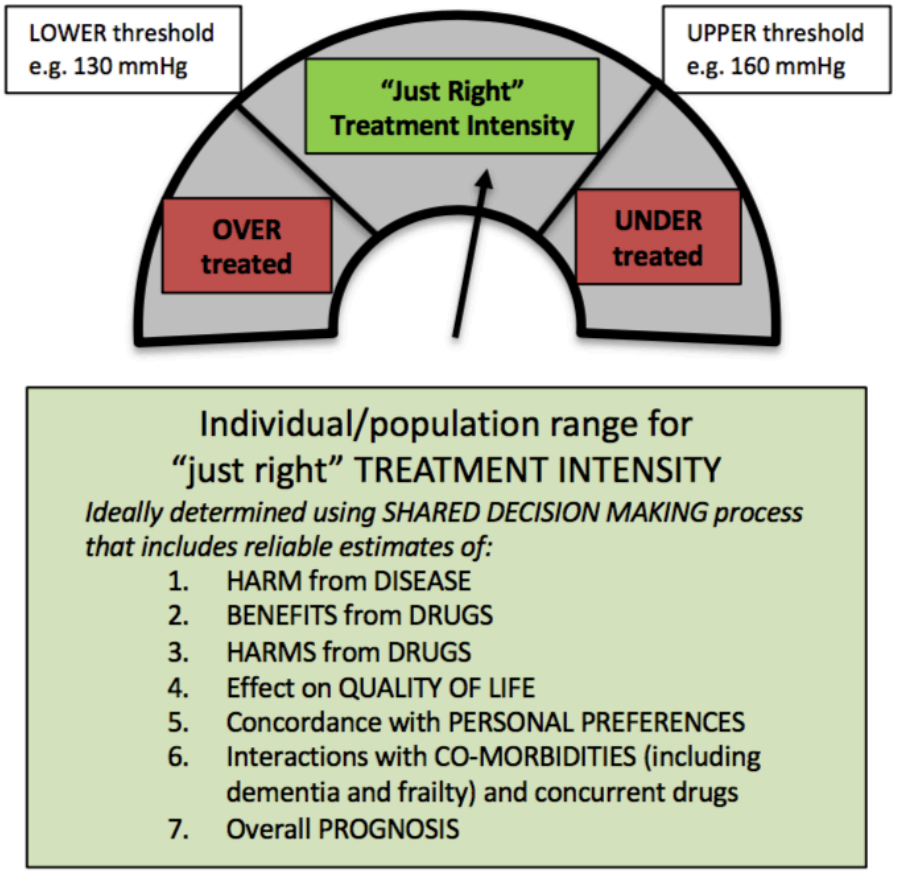


Figure 2.3 Example of potential integration of lower and upper systolic thresholds for hypertension clinical practice guidelines

For patients like Mrs. B, being able to estimate the harms and benefits of treatment between an upper and lower SBP threshold, in the context of her multi-morbidity, frailty, and dementia may have reduced her drug burden earlier. At this time, there are few studies that consider a lower threshold to be able to present such a decision tool. Making a reasonable estimate of the possible harms and benefits associated with varying levels of treatment intensity is necessary for informed shared decisions at a clinical level.

2.7 Concerns raised by observational studies of hypertension treatment

In contrast to the large randomized controlled trials finding benefit from treating hypertension, and that largely inform CPG's, some observational studies have found that certain lower levels of blood pressure are unexpectedly associated with negative outcomes such as increased rates of cognitive decline or death. The following paragraphs will provide an overview of these studies.

Globally, there are several large cohort studies of older people, collecting comprehensive datasets[158–161] and investigators have published reports noting inverse relationships between some surrogate measures and mortality and morbidity. For example, the Leiden 85 plus study has been following people over 85 years old in Leiden, Netherlands since 1987. They have an ongoing recruitment process that has resulted in approximately 85% of the population being included and have found inverse relationships between systolic blood pressure and negative outcomes[159] where people 90 years old with a SBP ≤150 mmHg have a 1.62 increased mortality risk than if SBP

>150 mmHg.[162] The Milan 75+ Cohort Study, which recruited from a community-based sample in a similar manner to the Leiden 85 study, reported a mortality HR 1.64 (95%CI 1.21-2.23) for SBP <120 mmHg and HR 1.32 (95%CI 1.10-1.60) for SBP 120-139 mmHg.[161]

A ten-year UK cohort study of 11,167 community-dwelling adults ≥70 years old found that one year unadjusted survival for those people with index SBP >120mmHg was 97.1% compared to 83.6% in those with index SBP <100mmHg. 69.5% of those with a SBP <100 mmHg (n=128 (1.2% of sample)) were taking at least one antihypertensive.[163]

The Ravindrarajah study, reviewed in section 2.2.1, found that mortality in people ≥80 years old was lowest with SBP 140-159 mmHg and mortality was 2-3 times higher when SBP was <120 mmHg.[112] Being treated with antihypertensive agents, or not, did not modify these results. This is similar to findings from Shih et al. which included a cohort of 128,765 people ≥65 years from the Taipei City Elderly Health Examination Database that found the adjust risk of all-cause mortality to be higher for SBP <110 mmHg, HR 1.12 (95%CI 1.05-1.20) when compared to 130-139 mmHg.[164] Odden et al. used NHANES data to examine blood pressure and mortality risk based on walking speed. They found that for participants who could not complete the specified walking test a SBP ≥140 mmHg was associated with a lower risk of death (HR 0.38 (95% CI 0.23-0.62).[165]

These observational study results are not concordant with the RCTs which raises questions about both representativeness of trial participants, as presented in section 2.4, or possible bias associated with observational studies.

2.7.1 Dementia and treatment intensity of hypertension

Dementia is a progressive disease that has a large effect on quality of life, morbidity, mortality and health care resource consumption. Prevalence of dementia increases with age and in Canada, a 2016 report from the Alzheimer Society of Canada said that in 2014, 514,000 people over the age of 65 had dementia at a cost of $9.5 billion in direct and indirect costs.[166] Our available treatments have only modest disease modifying potential in a fraction of those affected.[83] Being able to modify potential risk factors for development and/or progression of cognitive disease would be of great interest to society in general.

Hypertension, and systolic blood pressure in particular, and their relationship to incidence and progression of dementia have been closely studied. However, the resulting conclusions are mixed.[167–174] There have been analyses of both blood pressure levels and risk of dementia as well as antihypertensive treatment and risk of dementia. Few studies have specifically looked at levels of treated blood pressure and risk of dementia. The SPRINT trial[101] included an arm to specifically examine the associations between blood pressure treatment and cognitive function, but publication of results have been delayed and are now expected in 2019.[174]

In the meantime, a 2009 Cochrane review looked at 4 trials (HYVET,[176] SHEP,[177] SystEur[178] and SCOPE[179]) that included people over the age of 60 and concluded that there was not sufficient evidence to support lowering blood pressure in older people to prevent cognitive decline.[171] A more inclusive systematic review of 18 observational studies by Power et al. in 2011[169] had similar findings. Rouch et al. produced a review of 38 studies in 2015 examining the link between hypertensive medication use and cognitive decline found possible associations of protection from cognitive decline due to specific hypertension medications but note the lack of homogeneity of study designs and populations studied to be a barrier to definitive conclusions.[174] In summary, the quality of evidence to guide a treatment discussion of the dementia-related harms and benefits of hypertension treatment, to a particular systolic blood pressure target, is limited.

2.8 Hypertension treatment intensity among older people

The preceding sections of this chapter have explained why it is appropriate use hypertension as an example asymptomatic condition to explore the relationship between treatment intensity and polypharmacy. Hypertension's prevalence, robust experimental and observational research history, frequently collected surrogate measure of blood pressure and widespread CPGs provide an opportunity to explore the concept and postulate about potential implications of positive or negative findings.

As outlined above, despite accumulated evidence, clinicians do not have population-specific estimates of benefits and harms that might be made when hypertension is treated in people ≥70 years old, particularly those that are frail and/or have dementia.[120] Table 2.4 shows the how current guidelines relate to treatment intensity compared to the proposed new approach. The red areas of the table indicate current absence and the yellow areas, the proposed new aspects of treatment intensity definition.

Table 2.4 Current versus proposed approach to hypertension treatment intensity to be used in clinical practice guidelines

	CURRENT GUIDELINE DEFINITIONS		PROPOSED TREATMENT INTENSITY APPROACH e.g. hypertension	
	Observed	***Patient Experience***	***Observed***	***Patient Experience***
Undertreatment	Blood pressure ABOVE certain threshold	Harms of disease increased	Blood pressure ABOVE upper threshold	Harms of disease more than tolerable
"Just right" treatment	Blood pressure BELOW "target" threshold	Harms of disease decreased	Blood pressure BETWEEN upper and lower threshold	Both harms of disease & treatment are minimized according to patient preferences
Overtreatment	Not defined	Not defined, may have reference to "clinical judgement"	Blood pressure BELOW lower threshold	Harms of treatment more than tolerable

The above modifications to guideline recommendations could facilitate the work of a diligent clinician, caring for a patient like Mrs. B, and directly raise the idea that there may be relevant evidence to support reduction or discontinuation of treatment for hypertension.

2.9 Summary

Hypertension is a prevalent condition and treatment decisions and surrogate measure targets are common for people ≥70 years old. Unfortunately, an accurate estimate of the harms and benefits associated with antihypertensive treatment, particularly for those with co-morbidity or frailty, is not available. Despite this, CPG's emphasize particular systolic blood pressure treatment targets for all adults, regardless of their overall health status. There is a possibility that hypertension is being treated to levels of systolic blood pressure that may have increased harms and contribute to polypharmacy. Awareness and definition of various treatment intensities may help improve patient care.

Chapter 3: Association between polypharmacy and treatment intensity of asymptomatic conditions in nursing home patients

3.1 Overview

***What is already known*:** Polypharmacy is highly prevalent in Canadian nursing home patients.[180] Multi-morbidity is also highly prevalent,[181] and concurrence of multiple diagnoses may result in higher numbers of medications.[182]

***What this study adds**:*

1. I describe how hypertension and diabetes are treated for a randomly selected sample of 214 nursing home patients using a linked data set of patient charts, acute care utilization data and dispensed medications.
2. I describe numbers of medications prescribed and whether treatment intensity was associated with polypharmacy, or independently associated with treatment intensity for those single diseases. Both diabetes and hypertension were found to have a higher prevalence of lower surrogate markers than expected. General polypharmacy was also found to be associated with more intense disease-specific treatment.

***Limitations**:* This is a small study from a relatively contained geography in a single Canadian province. The study used only single readings for blood pressure and glycosylated hemoglobin, having multiple measures over time would improve accuracy. There are no consensus definitions of what constitutes overtreatment for hypertension

and diabetes, this study used an arbitrary starting point that maybe inaccurate or contentious.

Link to overall thesis: This study generated the hypothesis that an increased amount of treatment intensity for an asymptomatic condition may be related to increased polypharmacy an older nursing home older population.

3.2 Introduction

The right amount of treatment for frail elders living in nursing homes is a complicated formula that includes awareness of a patient's experience of quality of life, personal values and thorough knowledge of the capability of our modern medical interventions. Concern regarding possible harms of excessive prescribed medication has evolved into a field of study captured by the umbrella term "polypharmacy". Observational studies have shown associations between polypharmacy and adverse events such as hospitalizations and falls.[183]

Thus far, studies designed to reduce polypharmacy have typically used interventions to reduce overall numbers of drugs, or avoid certain categories of drugs thought to be inappropriate.[184] To date, we lack both a consensus definition of polypharmacy[23] and reliable tools to affect polypharmacy and improve patient outcomes.[32,185] To our knowledge, no previous studies examine the potential role of greater treatment intensity (i.e. attempts to achieve lower blood pressure in people with hypertension or lower A1c in people with diabetes) as potential reasons for polypharmacy. Diabetes and

hypertension are prevalent and lend themselves well to an exploration of treatment intensity as those conditions have routinely collected surrogate markers (e.g., systolic blood pressure and A1c) that give an objective measure of treatment intensity.

3.3 Project Objectives

The objective of this study was to examine, within a typical sample of nursing home patients, whether polypharmacy associates with lower surrogates – and in particular, whether it associates with blood pressure and A1c below a threshold which might be considered overtreatment of diabetes and hypertension in such a frail population. This exploration may suggest a relationship between overtreatment and more general polypharmacy tendencies which could serve as an adjunct to current approaches that identify unnecessary medications and facilitate deprescribing.

3.4 Methods

3.4.1 Setting and Participants

This is a cross-sectional study of a sample of 220 nursing home patients in Vancouver, Canada. The patients resided at one of six not-for-profit nursing homes (total population 954 patients) that share a similar clinical staffing and pharmacy model. The random sample was selected using an automated program to provide proportional representation from all six facilities. Participants were eligible to participate based on admission to facility on date of initial data gathering. The University of British Columbia-Providence Health Care clinical research ethics board approved the procedures of this minimal risk study and waived the requirement of patient consent.

3.4.2 Data Sources

Previous studies have established typical measures related to prevalence of polypharmacy and were used here as a framework for data collection.[186] Prescribing data from the hospital pharmacy on a single date (June 24, 2014) was augmented with patient demographics, medical history and chronic disease diagnoses from the patient's paper chart (collected July-November 2014). Acute care system use (emergency department visits and hospital admissions) for the subset of patients admitted prior to the date of pharmacy data collection (n= 147) was obtained from a local health authority database (October 2014). These three data sources were linked using a unique identifier. Appendix B provides details about the specific data collection and how data sources were linked.

3.4.3 Variable definitions

Disease diagnoses, frailty and hospital transfer status

The included facilities do not use an electronic medical record and the available paper chart diagnosis summary sheet was variable in its completeness. However, the disease diagnoses of interest for treatment intensity, namely hypertension and diabetes, have a locally available incentive fee code that requires regular documentation.[187] Dementia is often the disease that necessitates nursing home placement and was anticipated to be reliably noted. Congestive heart failure was identified using: a) mention on the diagnosis summary sheet; and/or b) prescription of furosemide[188] and was included to identify alternative reasons for observations of low blood pressure.

Systolic blood pressure (SBP) and glycosylated hemoglobin (A1c) were single readings recorded from the paper chart within 30 and 90 days, respectively, prior to the pharmacy data collection date. Given the anticipated issues with completeness of the paper chart medical history documentation, additional description of morbidity for the sample is provided with: a calculation of frailty, and hospital transfer status. The Canada Health Study of Aging-Clinical Frailty Scale (CHSA-CFS)[73] was calculated using standard functional assessments made by facility therapists. Possible scores are from 1-9, ≥7 is severely frail. Frailty score calculation was not possible for those who died during data collection (n=35). “Do not hospitalize” status was included to provide information about shared patient/family and provider expectations of medical intervention and was identified by re-coding of a standard health authority “do not attempt resuscitation” form.[189]

3.4.4 Polypharmacy definition and medication counting

Polypharmacy was defined as taking ≥9 regular medications, as this measure has often been used in previous nursing home prevalence studies.[180,186] Regular medications, the sum of which equals the polypharmacy measure, is defined as all regularly prescribed items requiring a physician’s order, regardless of route and including vitamins and supplements. This definition was selected for the main analysis to describe both regimen complexity and resources required by facilities to dispense and monitor medications.[19]

3.4.5 Treatment intensity and overtreatment definitions

For the purpose of this study we wished to identify patients whose surrogate measures were lower than the ideal for such a frail, end of life population. Excessive treatment of diabetes was defined as taking at least one hypoglycemic medication and having an A1c of ≤7.5. This A1c threshold was chosen as evidence suggests lower A1c is associated with a higher risk of serious harm due to hypoglycemia than potential treatment benefit.[190] Overtreatment of hypertension was defined using a study of frail elders by Mossello et al.[191] who found that an older (mean age 79) cohort of cognitively impaired (mean MMSE 22.1) people had increased harm for an accelerated cognitive decline if SBP was ≤128 mmHg (MMSE reduction -2.8 points versus -0.7 with higher SBP (p=.003)). A measure of polypharmacy, independent of disease specific treatment, was created by subtracting the number of disease specific medications from the total number of prescribed medications. This allowed exploration of a potential causal relationship between disease-specific overtreatment and more general polypharmacy prescribing tendencies.

3.4.6 Analysis

Previous reported estimates of population prevalence of polypharmacy have had wide variation (2%–91%).[186] Therefore, we used an estimate of prevalence of 50%, based on previous unpublished quality work done in the region, to calculate a sample size of 220 that would provide a precision level of 5%–6% with a 95% CI.[192] Descriptive statistics were used to describe the study population according to polypharmacy status, and the prevalence of polypharmacy and diabetes and hypertension. Tests of association used

analysis of variance (ANOVA), unpaired t-tests, χ^2 and Mann-Whitney U test, where appropriate. Values of $p<0.05$ were considered statistically significant. All statistical analyses were performed with IBM Statistical Package for the Social Sciences software (V.24.0; IBM).

3.5 Results

Data gathering was completed for 214 patients (6 died between date of randomization and accessing paper charts). Demographic and medical history characteristics of the study participants are presented in Table 3.1. The mean number of regular medications prescribed was 8.7 (SD ±3.9, 95% CI 8.2-9.2). Possible associations between facilities or prescribing doctors and the mean number of medications were assessed using an ANOVA calculation and were not statistically different.

Table 3.1 Patient characteristics by polypharmacy status

Characteristic	≤8 medications (n=110)	≥9 medications (n=104)	*P value*
Age in years, mean ±SD[&]	86 ± 9	84 ± 10	*p=0.72*
Male, n (%)	33 (30)	34 (32)	*p=0.67*
Length of Stay in nursing home in days, Median (IQR) [&]	861 (276, 1905)	741 (274, 1721)	*p=0.50*
Frailty score (CHSA-CFS)*, Median (IQR)	n=93 7 (7,7)	n=86 7 (7,7)	*p=0.73*
Dementia, n (%)	78 (71)	59 (57)	*p=0.03*
Hypertension, n (%)	72 (66)	81 (78)	*p=0.04*
Congestive heart failure, n (%)	10 (9)	25 (24)	*p=0.003*
Diabetes, n (%)	24 (22)	33 (33)	*p=0.07*
Systolic blood pressure, mmHg, mean ±SD	126 ±18	127 ±18	*p=0.54*
Diastolic blood pressure, mmHg, mean ±SD	66 ±12	66 ±10	*p=0.94*
A1c†, % Median (IQR)	n=28 6.2 (5.9, 7.0)	n=46 6.2 (5.6, 6.7)	*p=0.43*
Do Not Hospitalize Designation (stay at facility for all care, even in case of acute illness), n (%)	35 (32)	27 (26)	*p=0.35*

[&] mean and standard deviation (SD) are used to describe normally distributed data and median and interquartile range are used for non-normally distributed data.
* Calculation of Canada Health Study of Aging-Clinical Frailty Scale (CHSA-CFS)[73] was done October-November 2014, data are missing for 35 participants due to their deaths and subsequent loss of chart access. A higher score=increasing frailty; ≥7 is severely frail.
† A1c measured on 74 patients, but only 57 have a diagnosis of diabetes.

Acute care health services use (hospital admissions and emergency department (ED) visit) were analyzed for those patients who were admitted to the nursing homes during the 365 day acute care use data collection period, n=147. There was no difference in acute care service use between those with polypharmacy versus not. Of the 147 included patients, 117 (80%) had no transfers to the ED and 128 (87%) had no hospital admissions.

Blood pressure measurements were available for all patients in this sample, 92% had a SBP of ≤150 mmHg, 60% ≤130 mmHg. There was no significant difference in mean SBP between those patients with or without a diagnosis of CHF. At least one hypertension medication was prescribed to 120 people, 16 of those did not have a diagnosis of hypertension in their chart. Eighty-five percent of the patients with diabetes had an A1c ≤8.5%, 74% had an A1c ≤7.5% and 26% had an A1c ≤6%.

In figure 3.1, each dot represents an individual's systolic blood pressure (mmHg) and total number of hypertension medications prescribed. The horizontal line inserted on the figure is for 128 mmHg, the value that was used to determine overtreatment.[191]

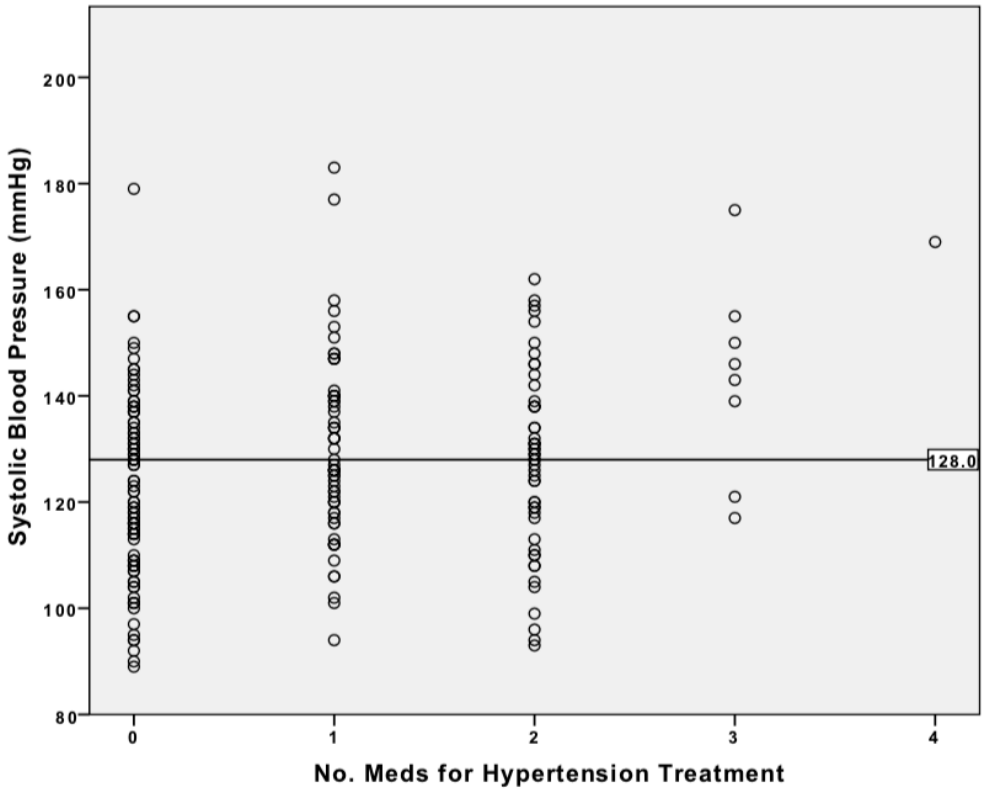


Figure 3.1 Systolic blood pressure and number of hypertension treatment medications

3.5.1 Prevalence of overtreatment and association with polypharmacy.

Twenty-five of the 57 patients with a diagnosis of diabetes were prescribed at least one regularly dosed hypoglycemic medication, and 13 of these 25 (52%) patients met our definition of overtreatment (A1c ≤7.5%).[190] The mean number of hypoglycemic drugs did not differ between the treated and over treated groups (1.5 ±1.2 versus 2.1 ±0.6). Of the 153 patients with a listed diagnosis of hypertension, 110 were prescribed at least one hypertension treatment medication, and 48 (44%) met the study-defined criteria[191] for overtreatment (SBP ≤128 and ≥1 hypertension medication). The mean number of hypotensive drugs did not differ between those treated and over treated (1.9 ± 0.9

versus 1.9 ±0.8). Table 3.2 presents two measures of association between overtreatment and polypharmacy. In patients with diabetes, those over treated received 3.8 more medications (excluding hypoglycemic medications) compared to those not over treated. For hypertension the over treated patients received 0.7 more medications but this difference was not statistically significant.

Table 3.2 Diabetes and hypertension overtreatment and associations with polypharmacy

a. Diagnosis of disease and polypharmacy

Patients with presence of disease diagnosis in chart	Regular meds ≤8	Regular meds≥9	Relative Risk (95% CI)	p value (z statistic)
Overtreated diabetes‡	2/24 (8.3%)	11/33 (33%)	4.00 (0.97-16.41)	0.054
Overtreated hypertension§	16/72 (22%)	32/81 (40%)	1.77 (1.07-2.96)	0.027

b. Intensity of disease-specific treatment and general polypharmacy

Patients receiving at least one drug for disease treatment	Total medications prescribed MINUS hypoglycemic drugs‖, mean ±	P value (t-test)
Overtreated diabetes, n=13	11.0 ±3.7	.01
Treated diabetes, n=12	7.2 ±3.1	-
	Total medications prescribed MINUS hypotensive drugs¶, mean ±SD	
Overtreated hypertension, n=50	8.4 ±3.8	.285
Treated hypertension, n=60	7.7 ±2.9	-

‡ Overtreated diabetes = having a diagnosis of diabetes, taking at least one hypoglycemic medication and having a A1c ≤7.5%[193]

§ Overtreated hypertension = having a diagnosis of hypertension, a *SBP ≤ 128 and hypertension medications ≥ 1*[191]

‖ where hypoglycemic drugs = biguanides, sulfonylureas, alpha-glucosidase inhibitors, any insulin and/or dipeptidyl peptidase-4

¶ where hypotensive drugs = angiotensin-converting enzyme inhibitors, calcium channel blockers, diuretics, β-blockers, angiotensin II type 1 receptor antagonists and α-adrenergic blocking agents, older agents including: methyldopa, reserpine and hydralazine were not found to be used in this cohort.

3.6 Discussion

This study demonstrates that polypharmacy is associated with a greater (potentially excessive) lowering of surrogates (SBP, A1c). Not surprisingly, and consistent with previous polypharmacy studies,[186,194] we found that patients prescribed ≥9 medications were more likely to have diagnoses of hypertension (p=.04) and CHF (p=.003).

Severe frailty and chronic disease treatment

The majority of this study's participants were severely frail (7/9 score on CHSA-CFS)[73] and had a diagnosis of dementia, which was expected given the strict requirements for nursing home admission in British Columbia. Clinical practice guidelines for older adults with hypertension and diabetes have begun to include discussion of frailty-informed treatment decisions with relaxed surrogate marker targets,[195,196] but lack specific thresholds for overtreatment or guidance on "de-intensifying". Our results show that 54% of treated diabetics have an A1c ≤7.5% and 44% of treated hypertensives have an SBP ≤128. In our view, frailty-specific guidelines that both identify a lower surrogate measure threshold that would define overtreatment and outline steps for deprescribing of blood pressure and glucose lowering drugs could be indicated in such patients.

Overtreatment as an indicator of inappropriate polypharmacy

We have demonstrated a statistically significant association between overtreatment of blood pressure and polypharmacy. We have similarly found an association between polypharmacy and overtreatment of blood sugar (4.0 RR) that borders on statistical significance ($p = 0.054$). Conceivably, these associations may be causal, with lower BP and lower A1c being indicators of a more aggressive overall treatment mindset on the part of the prescriber.

Harm reduction in the setting of polypharmacy has often focused on categories of "inappropriate" medications. However, recent research suggests that "appropriate" medications, such as those used to treat diabetes and hypertension, are more

frequently the cause of adverse drug reactions that result in emergency room visits and hospitalizations.[47] For patients ≥80 years old presenting to the emergency room with an adverse drug event, 15.2% (95%CI 11.4-19.0) were due to diabetic agents, whereas only 3.4%. were due to Beers criteria medications.[27] Focusing harm reduction on the intensity with which common medications are employed in the elderly might have as much (or more) utility than searching for drugs that are deemed inappropriate.

Limitations

This study took place in a single geographic region (British Columbia's lower mainland) and used a cross sectional format which provides only a "snap shot" observation of the data. Mortality rate is high in this population and loss of access to charts upon death affected some data collection. Inclusion of surrogate markers, A1c and SBP, are unique in this study however a limitation was having only a single measure for each. Measure-to-measure variability is common in this frail population, and a mean of at least three readings could have provided a more robust measure of treatment intensity, such as would be possible with a longitudinal design.

The definitions of overtreatment used in this study are arbitrary. Given the lack of current evidence on which to create such definitions, the specific thresholds used are debatable and will likely evolve for research purposes as new evidence emerges. They are proposed here, with rationale, as a starting point from which to reconsider the approach to polypharmacy. Finally, our sample size was not large enough to conduct more sophisticated statistical testing (e.g. regression modeling), therefore, there are

unmeasured variables that could also account for treatment intensity. We suggest more work needs to be done using a larger sample inclusive of a diversity of nursing homes and community dwelling residents.

3.7 Conclusions

Additional research that provides concrete quantifications of benefits and harms for ranges of treatment intensity are needed. In the meantime, this study is useful in two ways: 1) it suggests that overtreatment in this population may be quite prevalent and 2) that the presence of polypharmacy is to some degree associated with more intensive treatment of surrogate markers. Reduction in treatment-specific medications could both reduce potential of harms of overtreatment and reduce the overall number of prescriptions. Future studies to reduce polypharmacy and improve pharmacological appropriateness may benefit from consideration of treatment intensity for hypertension and diabetes.

Chapter 4: Treating hypertension in Canada: a cohort study of treatment intensity and polypharmacy for patients ≥70 years old

4.1 Overview

Relationship to overall dissertation: This chapter describes how hypertension in community-dwelling Canadians ≥70 years old is being treated by primary care clinicians. An accurate baseline measure could increase accuracy for estimates of the potential harms and/or benefits of interventions related to treatment of hypertension. This study also tests the hypothesis generated in Chapter Three: that greater treatment intensity of an asymptomatic condition increases general prescribing in a community-dwelling older population.

***What is already known*:** Hypertension is a risk factor for increased cardiovascular mortality and morbidity[176] and has been estimated to affect as many as 70% of Canadians ≥ 70 years old.[109] Multi-morbidity is also highly prevalent,[181] and concurrence of multiple diagnoses may result in higher numbers of medications.[182] Polypharmacy is a widespread concern in Canada, a 2012 study found 27% of people >65 years old had claims for 10 or more drug classes.[197] Polypharmacy has been linked to increased adverse drug reactions[198] and admissions to hospital.l[199]

What this study adds:

1. A detailed description of how hypertension is being treated in primary care for Canadians ≥ 70 years old, including types of drugs and resulting blood pressure measures.
2. An exploration of associations between intensity of hypertension treatment and rates of non-hypertension prescriptions (i.e. prescriptions for conditions other than hypertension), specifically the relationship between a treated systolic blood pressure (SBP) <120 or diastolic blood pressure (DBP) <70 mmHg and the numbers of non-hypertension prescriptions.
3. A comparison of the characteristics of the patients included in this study to those included in recent hypertension treatment trials to estimate ability to generalize RCT results to a non-experimental primary care population.

Link to overall thesis: Treatment of hypertension has rarely been considered as inappropriate or contributing to overtreatment. Observations about associations between hypertension treatment intensity and previously described forms of overtreatment, like polypharmacy, may help identify areas for effective interventions to reduce overtreatment.

4.2 Introduction

Hypertension is associated with increased cardiovascular morbidity and mortality.[105] Treatment of hypertension has been found to reduce these events in some studies;[102,176,200] however, there are concerns about the generalizability of the interventions to a heterogeneous population of older adults typically found in primary care, given trial exclusion criteria,[201] outcome selection[134] and selective results reporting.[202]

The recent SPRINT trial that compared hypertension treatment targets of 140 mmHg and 120 mmHg (introduced more fully in this dissertation, in Chapter 2), included a subset of community dwelling people ≥75 years, and found a significant reduction in a composite cardiovascular event outcome.[203] This has resulted in the Canadian hypertension guidelines now including a recommendation that “high-risk patients” be considered for intensive management to target a systolic BP <120mmHg.[204] This recommendation comes with specific caveats around who should be considered for the target (people with clinical or sub-clinical cardiovascular disease, chronic kidney disease, a 10 year global cardiovascular risk >15% or age ≥75 years old) and a description of the possible risks (e.g. hospitalization for electrolyte disturbance, acute kidney injury, etc). Having an accurate description of how hypertension is being treated in primary care and how the characteristics of the population compare to those included in randomized trials, like SPRINT, could improve estimates of possible population benefits and harms.

Existing published reports of hypertension treatment patterns in Canada are limited to descriptions of proportions of the population screened, diagnosed, treated and having a treated systolic blood pressure below 140 mmHg.[38,109,110] Having a more detailed source that describes specific use of drugs (number and type of agents) and details of resulting effects, including systolic blood pressure (SBP) <120 mmHg, diastolic blood pressure, pulse pressure, and coefficient of variation may give a more detailed description that could explain variation in expected treatment effects between people enrolled in trials and those treated more generally in primary care.

The results from Chapter 3 described a significant association between the most intense treatment of hypertension and increased non-hypertension polypharmacy in frail, nursing home-dwelling older people. If this association is found in a larger, community-dwelling sample it could help clarify the possible reasons behind polypharmacy and direct future research to reduce unnecessary prescribing or overtreatment.

4.2.1 Research Questions Addressed by this Study

This study addressed two questions regarding blood pressure treatment for community dwelling Canadians ≥ 70 years old, observed over a two-year period.

1) How is blood pressure treated in Canada? and

2) What are the demographic and health status characteristics and quantities of non-hypertension prescribing that are associated with having “most intensely treated”

hypertension (defined as blood pressured treated to SBP <120 mmHg or DBP <70 mmHg)?

Data are presented using the four systolic blood pressure categories in the 2017 Canadian Hypertension Education Program guideline[96] and include: patient characteristics, which medications are used to treat blood pressure the resulting measures of systolic and diastolic blood pressure, pulse pressure and coefficient of variation of blood pressure.

4.3 Methods

4.3.1 Study design and data source

Data for this cohort study were obtained from the Canadian Primary Care Sentinel Surveillance Network (CPCSSN), which provided a representative sample of community-dwelling older adults being treated for hypertension.[205] CPCSSN is a network of networks across Canada, where primary care clinicians voluntarily participate in electronic medical record extraction of de-identified data for the purposes of chronic disease surveillance, quality improvement and approved research purposes. It is an actively growing database of clinical data on primary care activities for over 1.6 million Canadians across seven provinces, who receive care from the more than 1400 participating family physicians and nurse practitioners (sentinels).[10]

Each patient record includes age, sex, CPCSSN validated diagnoses[206] (including: hypertension, diabetes, osteoarthritis, depression, dementia, epilepsy, Parkinsonism, chronic obstructive pulmonary disease (COPD)), all ICD-9 diagnostic codes associated with primary care billing and drug prescriptions (categorized according to World Health Organization's Anatomic Therapeutic Chemical (ATC) Classification System codes[207]). A complete description of the precise ICD-9 codes, free text entries, medication prescriptions and lab results are available at the CPCSSN.ca website.[208] The project received ethics approval from the Providence Health Care's UBC Clinical Research Ethics Board. A consent waiver was granted because the data are anonymized.

4.3.2 Participants

Inclusion criteria for the cohort required age ≥ 70 years, a diagnosis of hypertension, prescription of at least one renewed hypertension medication treatment and at least three measures of blood pressure during the observation period. Hypertension diagnosis used a validated algorithm[206] that included searches from diagnosis and billing codes, string text entries for both patient visits (encounters) and prescription data. Data for this analysis included eligible patients who were observed for two years. The specific start and end times for each participants' observation varied depending on their age and at what point the patient joined the participating clinician or when the clinician started using an EMR, whichever came first. Figure 4.1 describes how the observation time period was defined.

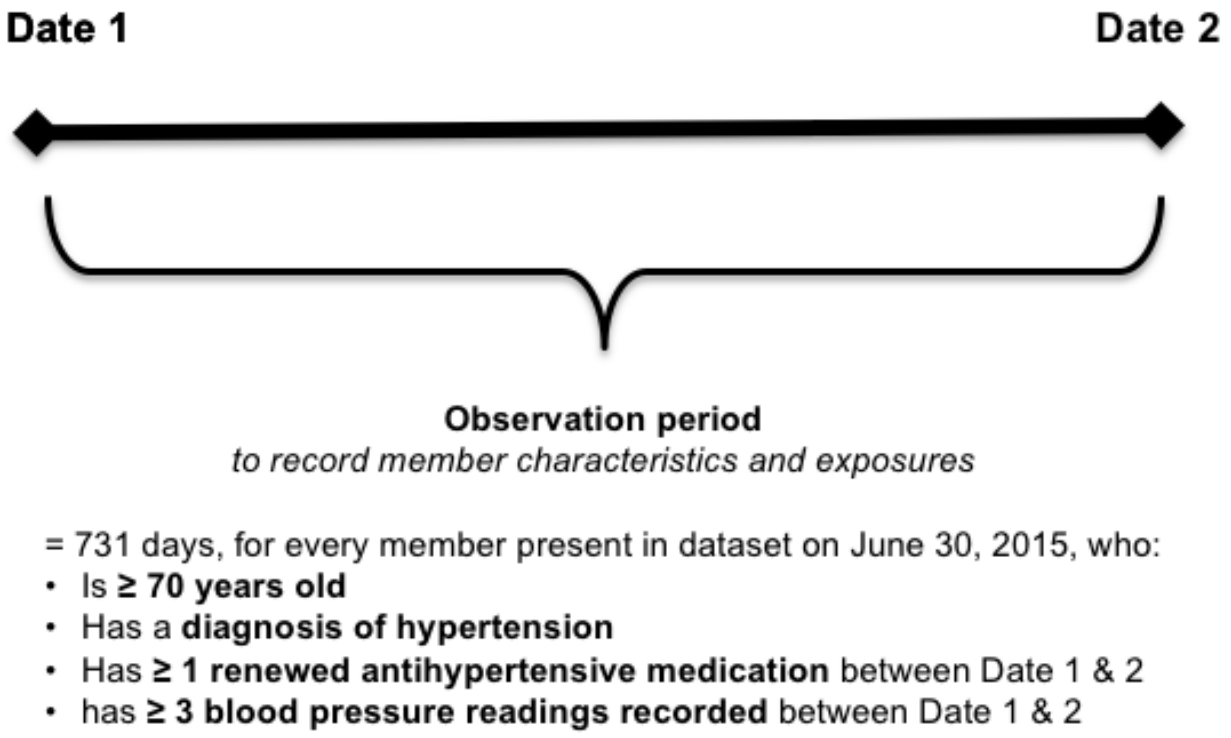


Figure 4.1 Definition of the cohort observation period and inclusion criteria

4.3.3 Patient characteristics and variables of interest

Patient characteristics, including: age, sex, weight, smoking status, LDL cholesterol and glycosylated hemoglobin (A1c) are taken directly from the patient record.

Hypertension diagnosis and antihypertensive medication therapy

Diagnosis of hypertension was determined with the CPCSSN algorithm, which uses a combination of diagnosis codes, EMR string text entries, and medication prescribing. This process has previously been shown to have sensitivity of 84.9%, specificity of 93.5%, and positive predictive value of 92.9%.[206] A participant was defined as having treated hypertension if prescribed at least one renewed hypertension medication during the observation period. Categories of drugs with hypertension medication effect were

identified from clinical practice guideline recommendations[209] and a meta-analysis of drug class effect on blood pressure.[210] WHO ATC codes[211] were used to identify prescription of these agents, where: C02 (Antiadrenergic agents), C03(diuretics), C07 (Beta Blocking Agents), C08 (Calcium Channel Blockers), C09 (Agents acting on the renin angiotensin system). See Figure 4.2 for a complete list. This list is more comprehensive than the list of drugs typically considered in published clinical practice guidelines for treatment of hypertension, as we wished to identify all drugs which may be lowering blood pressure.

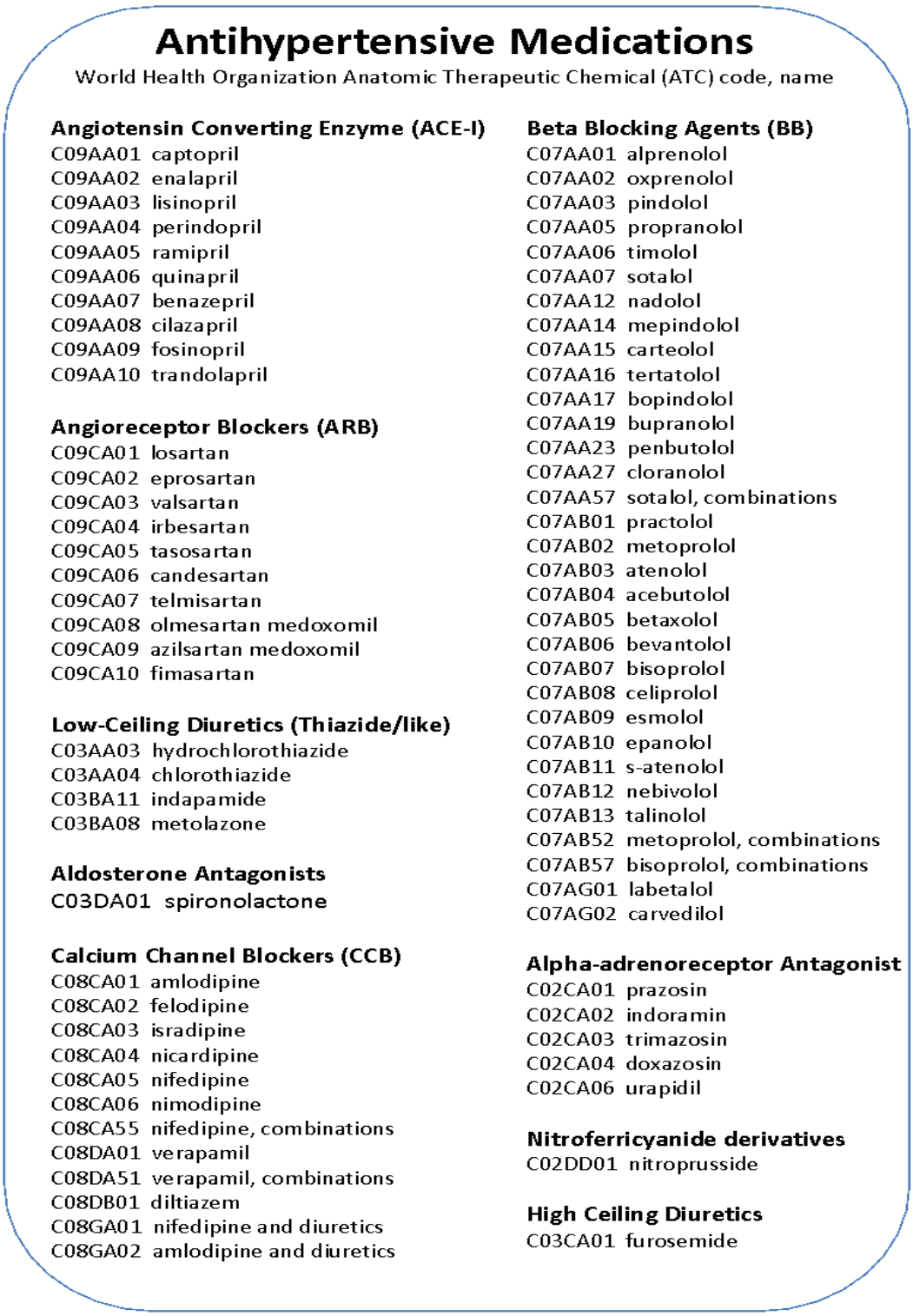


Figure 4.2 List of included hypertension medications

Blood pressure measures

Systolic and diastolic blood pressure (SBP and DBP) were taken directly from the patient clinical record and were reported as mean values. Inclusion criteria required at least 3 blood pressure readings over two years as this was felt to be the minimum frequency reasonable to accurately describe actual blood pressure and variation between readings. There is little published literature to guide this definition; however, reference to other studies that recorded blood pressure results suggested this was a reasonable minimum.[212–214] Similarly, we chose two years over which to make our observations as we felt this was a reasonable length of time for primary care providers to adjust drug therapy.

Treatment intensity

Categories of SBP were based on the 2017 Canadian hypertension treatment guidelines: <120, 120-140, 140-160 and >160 mmHg.[96] Hypertension treated to <120 mmHg was the lowest category used in the presented analyses as it is the lowest treatment target identified in the Canadian guideline. This category was referred to as having the highest treatment intensity.

Quantification of polypharmacy and antihypertensive drug counting

There is no gold standard for the definition of polypharmacy.[23] Many Canadian studies have used a cut-off of 9 medications or more to indicate polypharmacy.[180] CPCSSN prescription information is limited to date prescribed, agent, dose, frequency and

quantity for all agents that were prescribed, not those that were necessarily dispensed and consumed.

The total number of prescriptions written during the observation period was called “total prescriptions”. To count hypertension medication (complete list in Figure 4.2), we used the presence of a repeat prescription for the same agent, within the observation period, as a surrogate for confirmation that the prescribed medication was being dispensed and used. This process was not possible for all the non-hypertension prescriptions due the quantity and diversity of different drugs prescribed and the subsequent data programing requirements. As we were interested in the possible relationships between excessive prescribing for non-hypertension-related conditions and treated hypertension, we created a measure of non-hypertension prescribing which is equal to the total number of prescriptions during the observation period minus the total number of repeated hypertension medications. This quantity was called “total non-hypertension prescriptions” and was used in three ways: as a continuous variable, as a binary variable of <9 or ≥9; and quintiles.

Outcome and predictor variables

The study I carried out in Chapter 3 found an association between increased non-hypertension related prescribing when blood pressure was treated most intensely in nursing home patients.[7] To see if this relationship persisted in community-dwelling people, I used quintiles of non-hypertension medications as the independent predictor

variable and treated SBP <120mmHg or DBP <70mmHg as the dependent outcome variables.

Covariates for multivariate logistic regression model

Covariates were identified and included to adjust for potentially confounding effects. The literature was reviewed to identify which characteristics and disease states could be expected to be associated with lower blood pressure measures. Female sex, increasing age,[215] congestive heart failure[216] and Parkinson's disease[217] have all previously been found to be associated with decreased SBP and were included. Dementia has been found to be associated with higher blood pressure,[218] and hypertension treatment guidelines for people with known cardiovascular conditions and risk factors, including diabetes, often include lower SBP targets.[95,195] Depression has been hypothesized to be aggravated by low blood pressure[219] and osteoarthritis and COPD often require multiple prescriptions,[220] so these conditions were included to explore other associations.

Comorbidity information was collected directly from CPCSSN data using either a previously validated CPCSSN disease algoritms,[8,206] or a search for specific ICD-9 billing codes. ICD-9 code searches were added to better describe cardiovascular co-morbidities and included: congestive heart failure,[188] other cardiovascular disease and cerebrovascular disease. Diagnoses were considered present if recorded in the health record at least once in the baseline period. Figure 4.3 provides additional detail about identification of the comorbidities reported in this study, including specific ICD9 codes.

The number of changes to the electronic medical record is included as a surrogate measure of health services utilization, these changes to the record which include: visits to primary care, notes added by other team members, results from lab tests being added, etc and a larger number of changes are assumed to be associated with a higher level of co-morbidity.

Comorbidity Variable Name	Description	How created
Diabetes	Type 2 diabetes	CPCSSN algorithm
CHF	Congestive heart failure	ICD9 code 428.x or prescription of furosemide
Other cardiovascular disease	Includes: valvular disease, myocardial infarction, aortic aneurysm, atherosclerosis, peripheral vascular disease	410, 411, 412, 413, 414, 427, 441.4, 441.3, 441.9, 441.01, 443.9 or 440.21
Cerebrovascular disease	Includes: intracranial hemorrhage, stroke, cerebral artery stenosis, TIA, late effects of stroke	430, 431, 432, 433, 434, 435, 436, 437, 438 or V12.54
Dementia	-	CPCSSN algorithm
Depression	-	CPCSSN algorithm
Parkinson's Disease	-	CPCSSN algorithm
COPD	Chronic Obstructive Pulmonary Disease	CPCSSN algorithm
Osteoarthritis	-	CPCSSN algorithm

CPCSSN algorithm details available from: CPCSSN_DiseaseDefinitionsFINAL_July16-2014.pdf[208]

Figure 4.3 Comorbidity variable definitions and data sources

Burden of Illness

People being more sick, and generally unwell, is a possible explanation for having a lower blood pressure.[221] Ideally, we would calculate a standardized measure of co-morbidity (e.g. the Charlson Comorbidity Index[222,223]) to identify those participants who were more generally unwell. However, this calculation was not possible within the CPCSSN data. Instead, using a directed literature search and the variables available, we identified four variables that could help identify those participants with an increased burden of: the count of all co-morbidities of interest (Figure 4.3),[224] changes made to the medical record,[225] number of blood pressure measures and variation between an individual's SBP readings, expressed as the coefficient of variation.[226] Increased variability in blood pressure has been found to be associated with poorer prognosis and increased all-cause mortality.[213,226–229]

4.3.4 Statistical Analysis

Measures of central tendency and variation were examined for all continuous variables: mean and SD for normally distributed variables and median and IQR for non-normal results. All continuous variables were tested for normality of distribution using the Kolmogorov-Smirnov test. Comparisons of frequencies of patient characteristics between categories of SBP are presented using a t-test, analysis of variance (ANOVA), chi-squared or Kruskal Wallis tests, as appropriate.

We used a multivariate logistic regression model to assess the relationship between the dependent outcome variable, treated SBP to <120 mmHg or DBP to <70 mmHg, on the

independent predictor variable, numbers of non-hypertension prescriptions. At present there is insufficient evidence to say whether increased prescribing is the cause of a lower treated SBP/DBP or vice versa. This dataset allowed for a precise definition of treated blood pressure whereas our ability to describe prescribing was less precise. Therefore, we used treated SBP <120 mmHg or DBP <70 mmHg as the dependent outcome variable. Covariates in the model, including: age, sex, co-morbidities of interest and surrogate measures for burden of illness, were selected a priori due to what is known about their relationships with treated blood pressure and other prescribing.

In secondary analyses, we performed a sub group analysis by the presence or absence of ≥3 comorbidities and all statistical tests were performed using IBM SPSS Statistics for Macintosh, Version 24.

4.4 Results

A total of 25,737 cohort members with treated hypertension were included. Figure 4.4 shows how the inclusion criteria were applied to create our cohort.

4.4.1 Members of cohort

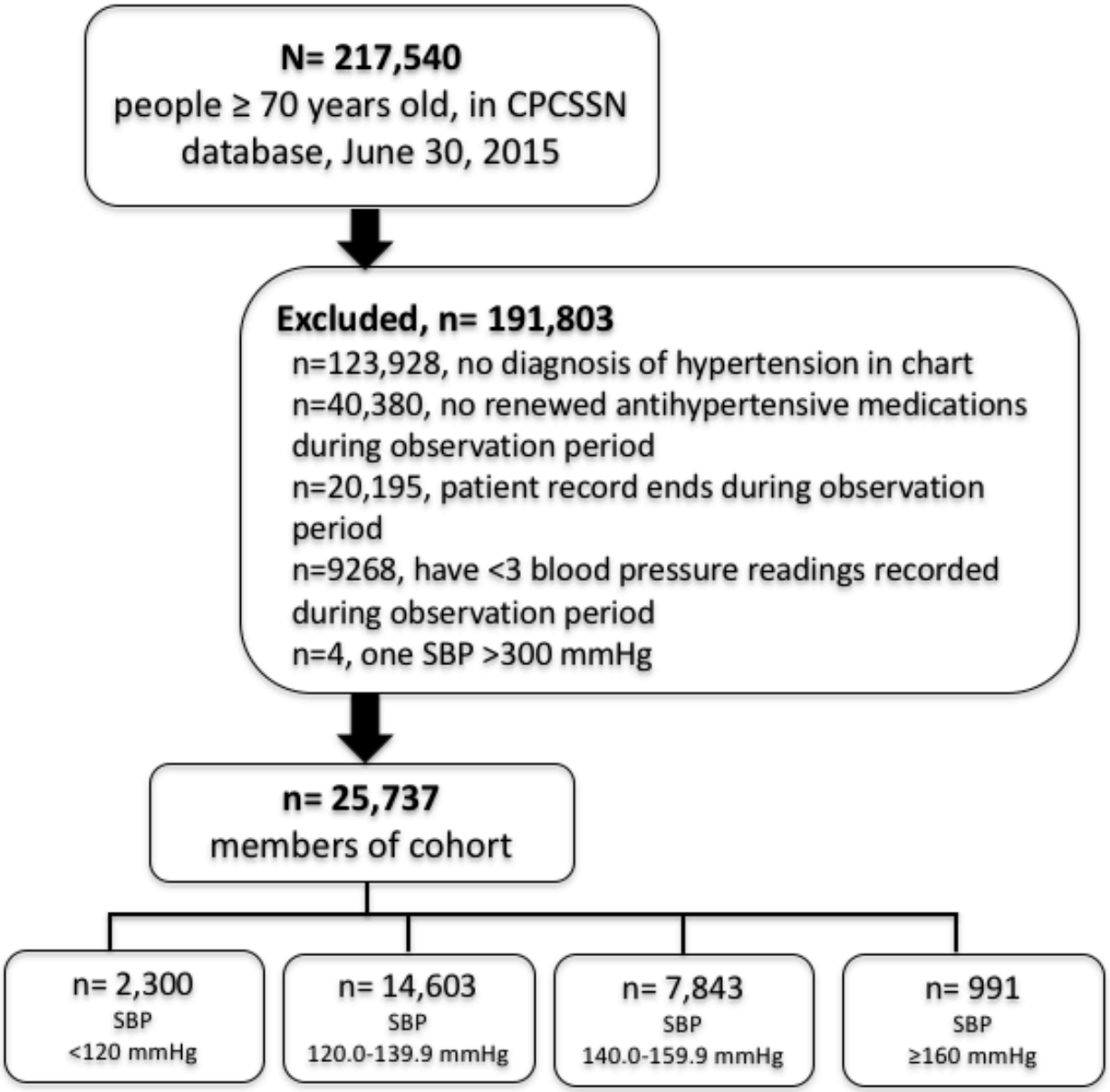


Figure 4.4 Cohort creation, flow diagram

4.4.2 Cohort Characteristics

The mean age of this cohort was 82.3 +/- 6.7 years and 61.2% were female. All variables reported in Table 4.1 were found to have normal distribution, with the

exception of number of: EMR record changes, hypertension medications and co-morbidities. Smoking data was missing for 17,560 (68.2%) members of the cohort. Weight, LDL and A1c were present for 22,856 (88.8%), 21,019 (81.7%) and 17,487 (67.9%) participants, respectively. Twenty-seven percent of participants (n=6937) had a concurrent diagnosis of diabetes and 3578 (14.6%) had CHF. Table 4.1 presents the cohort characteristics by SBP category.

When compared to the participants in the other three categories, participants with treated SBP <120 mmHg were more likely to be male (51.4%), current or past smokers (17.2%), and had higher rates of most co-morbidities, including the highest proportion of people (36.3%) with 3 or more co-morbidities (in addition to hypertension). This group was also more likely to receive ≥ 9 non-hypertension prescriptions (48.0%).

Table 4.1 Cohort characteristics, by systolic blood pressure (SBP) category

	SBP <120 mmHg	SBP 120-139 mmHg	SBP 140-159 mmHg	SBP >160 mmHg
Total participants, N=25,737, n (%)	2300 (9)	14,603 (57)	7,843 (30)	991 (4)
≥9 non-htn prescript. (polypharmacy), n (%)	1104 (48.0)	5416 (37.1)	2533 (32.3)	266 (26.8)
Age, mean ±SD	82.4 ±6.9	82.0 ±6.6	82.7 ±6.7	84.0 ±7.0
% female	1118 (48.6)	8696 (59.4)	5220 (66.6)	720 (72.7)
Female weight, (kg) mean ±SD	72.2 ±22.8	73.2 ±22.6	73.5 ±23.1	71.8 ±22.3
Male weight, (kg) mean ±SD	86.1 ±24.0	88.7 ±24.3	88.5 ±24.5	86.5 ±24.3
Smoking[#], Current or Past, n (%)	393 (17.1)	2073 (14.2)	1077 (13.7)	126 (12.7)
LDL, median, (IQR) n =21,019	2.0 (1.5,2.6)	2.3 (1.7,2.9)	2.6 (1.8,3.2)	2.7 (2.0,3.4)
A1c, % median (IQR) n =17,487	6.0 (5.7,6.5)	6.0 (5.7, 6.5)	6.0 (5.7, 6.4)	6.0 (5.7,6.5)
CONCURRENT COMORBIDITIES				
Diabetes, n (%)	730 (31.7)	4018 (27.5)	1931(24.6)	258 (26.0)
Congestive heart failure (=CHF), n (%)	633 (27.5)	2040(14.0)	962 (12.3)	123 (12.4)
Other cardiovascular disease, n (%)	781 (34.0)	3208(22.0)	1281(16.3)	136 (13.7)
Cerebrovascular disease, (incl. stroke) n(%)	113 (4.9)	700 (4.8)	303 (3.9)	29 (2.9)
Dementia, n (%)	407 (17.7)	2019 (13.8)	994 (12.7)	115 (11.6)
Depression, n (%)	426 (18.5)	2100 (14.4)	902 (11.5)	91 (9.2)
Parkinson's disease, n (%)	39 (1.7)	160 (1.1)	65 (0.8)	9 (0.9)
Chronic obs. pulm. dz. (COPD), n (%)	448 (19.5)	1907(13.1)	852 (25.9)	83 (8.4)
Osteoarthritis, n (%)	700 (30.4)	4382(30.0)	2382(30.4)	237 (23.9)
BURDEN of ILLNESS & BP MEASURES				
# health record changes, median, (IQR)	25 (16,37)	22 (15,33)	21 (14,31)	19 (13,29)
≥ 3 co-morbidities, n (%)	834 (36.3)	3297 (22.6)	1391 (17.7)	136 (13.7)
Co-efficient of variation for SBP, mean ±SD	0.09 ±0.04	0.08 ±0.04	0.09 ±0.04	0.10 ±0.10
Diastolic blood pressure, mmHg, mean ±SD	66.9 ±6.4	72.8 ±6.9	76.3 ±7.8	81.2 ±9.5
Pulse pressure, mean ±SD	47.3 ±6.8	58.5 ±7.9	70.8 ±9.0	87.2 ±11.4
# BP readings, median, (IQR)	7 (5,11)	7 (5,11)	8 (5,13)	7 (4,11)
ANTIHYPTERTENSIVE* PRESCRIBING				
1 antihypertensive medication n (%)	799 (34.7)	5848 (40.0)	2921 (37.2)	331 (33.4)
2 antihypertensive medications, n (%)	776 (33.7)	4904 (33.6)	2578 (32.9)	311 (31.4)
3 antihypertensive medications, n (%)	472 (20.5)	2579 (17.7)	1480 (18.9)	193 (19.5)
≥4 antihypertensive medications, n (%)	253 (11.0)	1272 (8.7)	864 (11.0)	156 (15.7)
Thiazide(-like) diuretics, n (%)	603 (26.2)	5525 (37.8)	3338 (42.6)	432 (43.6)
Angiotensin Convert. Enzyme Inhibitors, n (%)	1011 (44.0)	5809 (39.8)	3075 (39.2)	382 (38.5)
Angioreceptor Blockers, n (%)	575 (25.0)	3778 (25.9)	2278 (29.0)	327 (33.0)
Calcium Channel Blockers, n (%)	734 (31.9)	5836 (40.0)	3446 (43.9)	466 (47.0)
Beta blockers, n (%)	1114 (48.4)	5118 (35.0)	2572 (32.8)	384 (38.7)
Spironolactone, n (%)	130 (5.7)	268 (1.8)	118 (1.5)	17 (1.7)
Furosemide, n (%)	524 (22.8)	1670 (11.4)	779 (9.9)	94 (9.5)
Alpha-blockers, n (%)	28 (1.2)	155 (1.1)	120 (1.5)	16 (1.6)

Smoking data missing for 16,422 members of cohort

* Figure 4.2 has a complete list of hypertension medications that were included. If drug class was present more than once, was only counted once.

Blood pressure treatment measures and classes of prescriptions

Table 4.1 also provides a detailed description of blood pressure measures and classes of drugs used for treatment. The largest proportion of people being prescribed ≥4 classes of hypertension medications were those who had a SBP >160 mmHg (15.7%). For those in the lowest SBP category, there were the highest prescribing rates for furosemide (22.8%) and spironolactone (5.7%), which are often used in combination to treat congestive heart failure (CHF). For the entire cohort, frequency of prescription of classes of hypertension medications suggested by the Canadian Hypertension Education Program,[96] was as follows: thiazide 38.9%, ACE-I 39.9%, ARB 27.0%, CCB, 42.0% and beta blockers 36.7%. To assess for influence of a CHF diagnosis on prescribing patterns for hypertension, we removed the cohort members with a diagnosis of CHF and found these proportions were only slightly changed, where thiazide 41.4%, ACE 39.5%, ARB 26.7%, CCB 41.1% and for beta-blockers 33.4%.

Number of total prescriptions and comorbidity

An increase in the number of total prescriptions was significantly associated with having a higher number of disease diagnoses. An ANOVA ($p<.0001$) comparing the mean number of prescriptions to the sum of comorbidities (0 for just hypertension to a maximum of 9 comorbidities) shows the same pattern where an increasing number of diagnoses results in a higher mean number of prescriptions (Figure 4.5). The mean number of prescriptions for those participants with just hypertension (n=6824) versus

those with three or more additional comorbidities (n=5658) was 6.97 versus 13.25, t-test <.0001, mean difference 6.28 (95% CI 6.10-6.46).

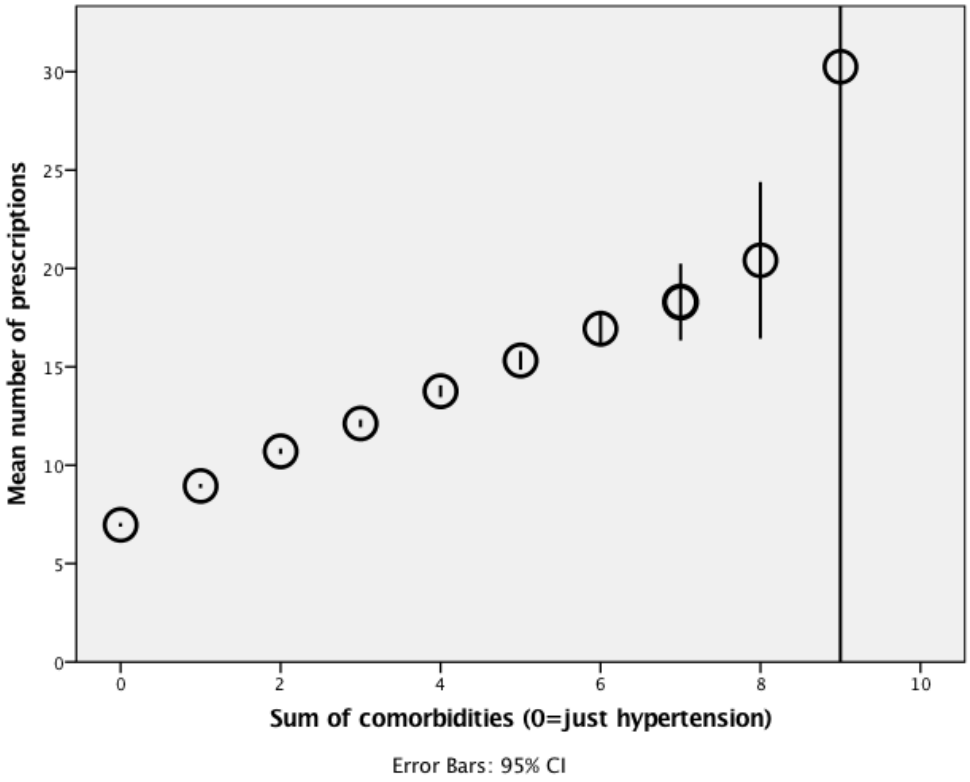


Figure 4.5 Mean of total prescriptions and number of co-morbidities in addition to hypertension

Figures 4.6 and 4.7 presents the adjusted logistic regression model results where the binary outcome of treated SBP <120 and DBP <70 mmHg were explored for associations with various participant characteristics. Less than or equal to 3 was used as the reference category for comparison with quintiles of non-hypertension prescriptions. A significant association was seen for all comparison quintiles in both SBP and DBP.

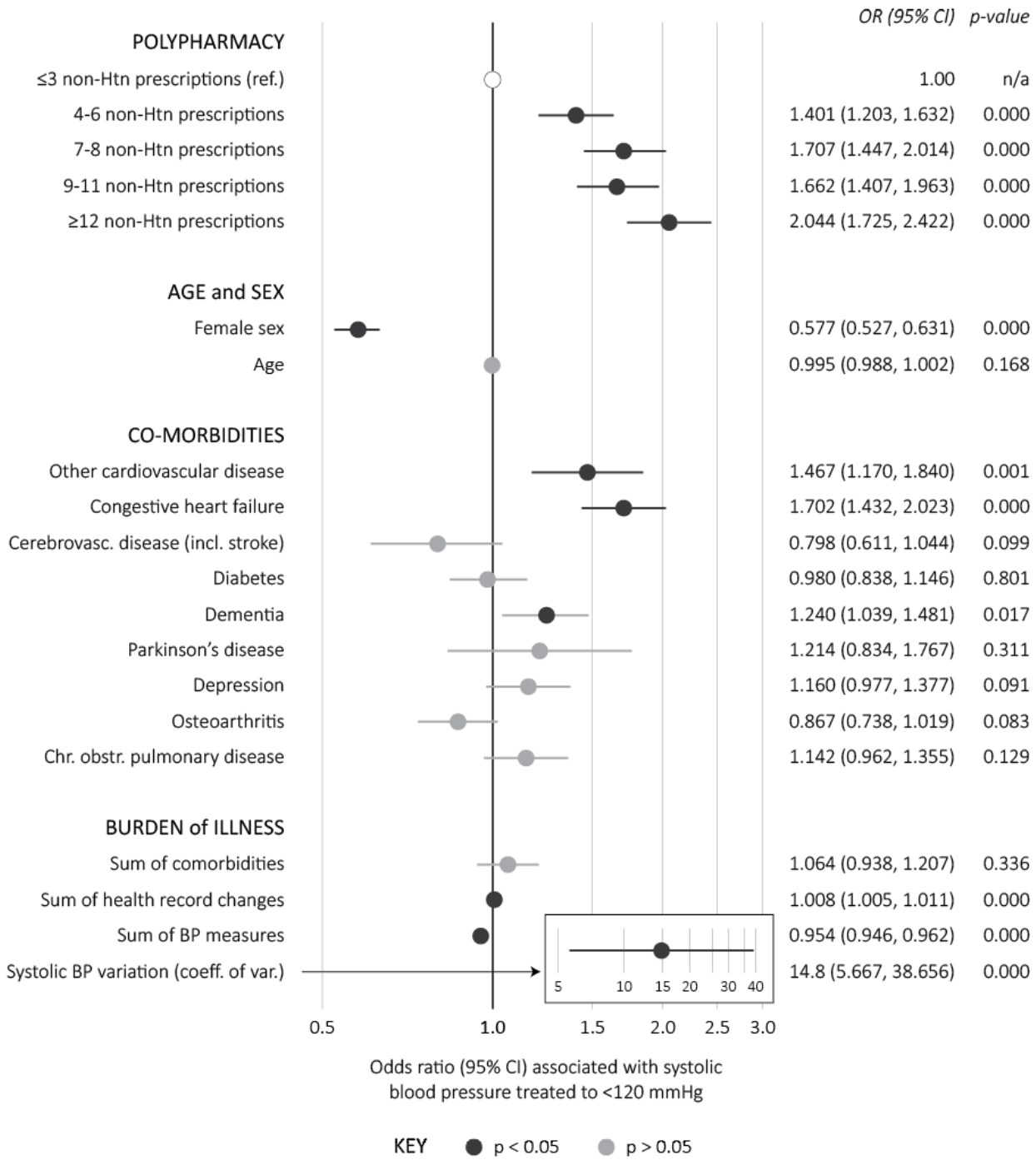


Figure 4.6 Multivariate logistic regression model: odds ratios associated with systolic blood pressure treated to <120 mmHg

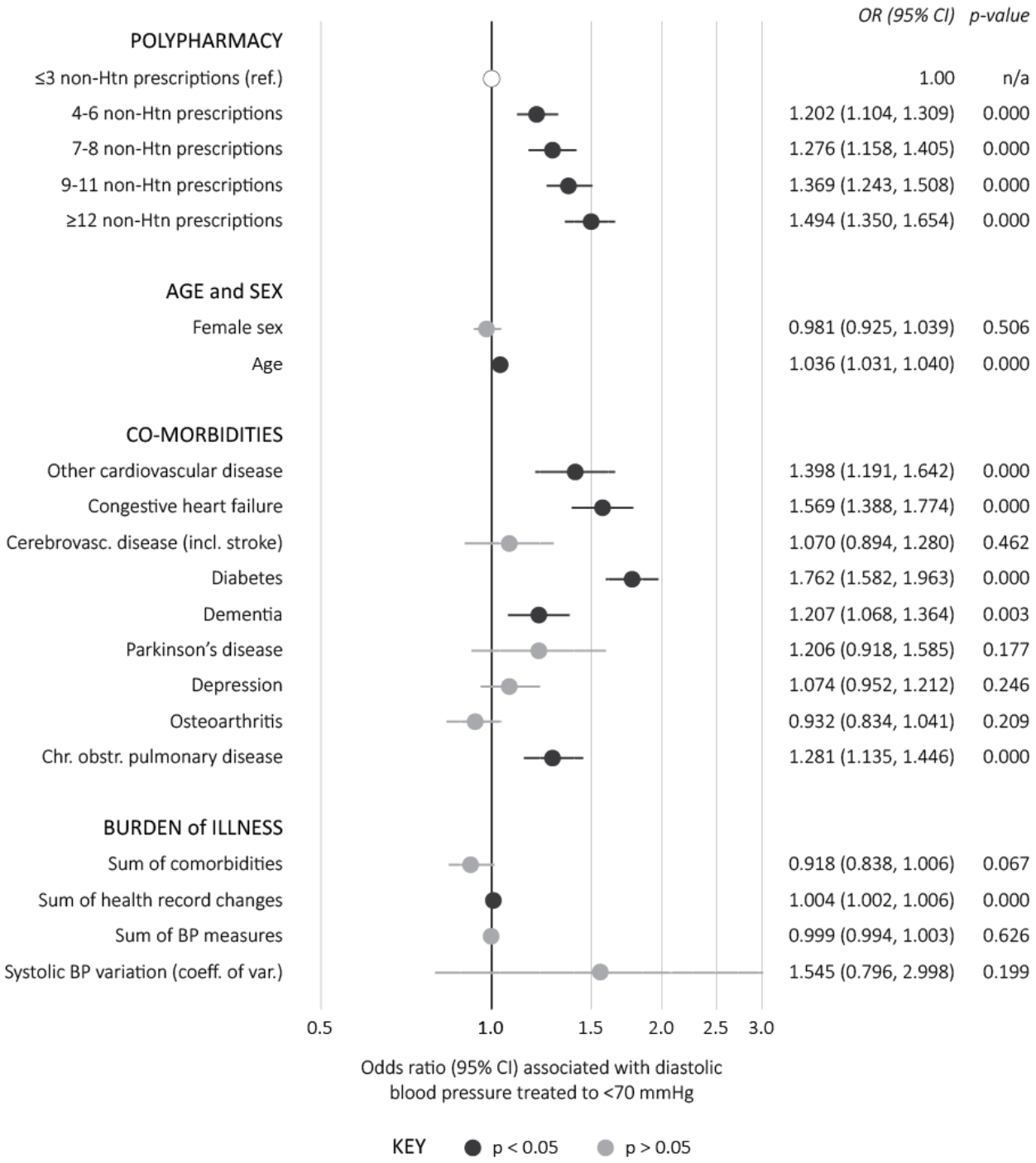


Figure 4.7 Multivariate logistic regression model: odds ratios associated with diastolic blood pressure treated to <70 mmHg

The logistic regression model found that having blood pressure that is treated to SBP <120 or DBP <70 mmHg was significantly associated with also receiving more non-hypertension prescriptions.

4.5 Discussion

In this study of more than 25,000 Canadians ≥70 years old, I found that having a treated SBP <120 or DBP <69 mmHg was associated with an increased likelihood of being prescribed more non-hypertension medications. Further, we found that 9% (2300) members of the cohort have a treated systolic blood pressure <120 mmHg, and also appear to be generally more unwell.

Association between treated systolic blood pressure and polypharmacy

To my knowledge, there is limited literature describing associations between polypharmacy and hypertension treatment intensity. Similarly, the exploration of how treatment of asymptomatic risk factors, like hypertension, may affect polypharmacy has only recently garnered attention.[230] Benetos et al. published a systemic review of hypertension guidelines for “very old and frail people” (≥80 years old) that included a discussion about the concern of polypharmacy and the potential contribution of hypertension medications to adverse effects,[231] but did not include any analysis demonstrating observed associations. Larger numbers of prescriptions for participants might be explained by a larger burden of illness (whether with chronic or symptomatic) and requiring more drugs on that basis, i.e. that those whose SPB is treated to <120

mmHg in this study are more unwell than the rest of the sample. This is potentially supported by the observations in Table 4.1 that there are more EMR record changes, more prescriptions, and a higher prevalence of dementia and depression. Most notably, the prevalence of CHF is almost twice as high as in any other category of blood pressure. If patients are more generally unwell, it may be the physiological processes that result in a lower blood pressure, rather than an intentional hypertension treatment strategy. The use of hypotensive medications may be used for treatment of symptoms, for example CHF exacerbations. However, the covariates used to describe burden of illness used in the logistic regression models did not show this, which could indicate a problem with the choice of variables or that the presence of ≥4 non-hypertension prescriptions, other cardiovascular disease and congestive heart failure are in fact better predictors of who will have a treated SBP <120 or DBP <70 mmHg.

Alternatively, it could be that the same philosophy of prescribing that results in someone having a treated SBP <120 mmHg or DBP ≤70 mmHg also translates to more aggressively prescribing for other conditions. At this time, I am unaware of any other literature identifying/exploring this relationship. If it is related to a “prescribing philosophy”, identifying a lower threshold above which the surrogate should remain could possibly translate to decreased prescribing for other conditions as well. For example, if a patient is being treated for hypertension with 25 mg of hydrochlorothiazide and 5mg of ramipril and has a blood pressure of 110/62 mmHg, a guideline that included both a lower and upper threshold for a treatment target, could advise considering discontinuing one or both of the prescribed medications, until the blood

pressure measurement is consistently between the lower and upper thresholds recommended. By reducing the treatment of blood pressure in this way, it is possible that the prescriber may give consideration to other prescriptions which may be "excessive". Previous drug class-specific deprescribing studies have not reported on effects on numbers of prescriptions for additional drug categories.[11]

Prevalence of systolic <120 mmHg or diastolic blood pressure <70 mmHg

Our cohort inclusion requirement of having 3 blood pressure readings over two years provides a level of detail regarding surrogate measure response to prescription treatment that has not been included in other observational studies of this size. Nine percent of this sample had a blood pressure ≤119 mmHg. In the UK, Ravindrarajah et al. found a similar proportion (9.3%), but of people >80 years old, with a diagnosis of hypertension.[112] They used a primary care database cohort of 144,403 people who were diagnosed with hypertension and 62% of who received treatment. They reported the median number of BP readings was 0.84-3.04 across the 20 categories included in their Supplementary Table 2. Morrisey et al. found 12.2% to have a SBP ≤119 mmHg, in a sample of 6912 primary care patients ≥70 with treated hypertension.[163] This work showed an increased association between death and a SBP ≤119 mmHg (OR 2.00-6.51), and also noted that for the 313 people with a treated SBP <100 mmHg, just 34% had a reduction (de-intensification) of their hypertension medications.

Regardless, everyone in this sample is receiving at least one hypertension medication which may be considered overtreatment if SBP is <120 mmHg. The work by Morrissey

et al. shows that older people with treated blood pressure <120 mmHg have increased mortality and hospital admission.[163] Shih et al. used a retrospective cohort of 128,765 people ≥65 in Taiwan, 34.1% who used hypertension medications and found a J-shaped curve for mortality, with increasing harm at ≤130 mmHg and ≥ ~150mmHg. There is conflicting observational evidence about the possibility of increased harms from blood pressure that is treated to a level that is either “too low” or “too high”. More research is needed to be able to accurately estimate harms and benefits of treatment of blood pressure to specific ranges.

Comparison of findings from similar studies

This study presents a detailed description of hypertension treatment by family physicians of Canadians ≥70 years old. Forty-three percent of the 217,540 people ≥70 years old in the CPCSSN dataset had diagnosis of hypertension. This is lower than a previous estimate of 62.6%-74.6% by Robataille et al. in a study[110] that used a similar method to identify people with hypertension, but whose sample came from different sources, including the Canadian Chronic Disease Surveillance System, which may have higher proportion of people with chronic diseases than are typically seen in a sample more representative of the general population.

Godwin et al. used an earlier dataset (June 2012) from CPCSSN to describe hypertension prevalence and treatment in Canada. While this paper provided a broad description of the frequency of diagnosis of hypertension and comorbidities, it included adults of all ages and those who did not have any blood pressure reading nor any

recorded prescriptions for hypertension medications. Just 79% of their sample had at least one recorded blood pressure and they found 79.8% to have SBP ≤140 mmHg and 94.5% to have DBP <90 mmHg. The difference between our results (65.7% with a SBP ≤140 mmHg) and theirs is likely due to those with a lower blood pressure and not being prescribed hypertension medications being excluded from our study.

Comparing this cohort to participants of recent hypertension trials

Generalizability of trial results to primary care populations is a well-described concern.[232] In this actively treated, community-dwelling primary care population, we found that 66.0% were treated to <140mmHg and 9.0% to <120 mmHg. There were no co-morbidity exclusion criteria and the 2-year observation period is similar to that typically used for hypertension trials. Table 2.3 in Chapter 2 summarizes the exclusion criteria from 5 studies that compare intensities of blood pressure treatment in older people (in this case via differing allocated BP targets). For example, the SPRINT study, which compared a “usual care” treatment target of <140 mmHg to <120 mmHg, had a diabetes exclusion criteria that would have removed 27.0% of our cohort. In general, individuals being treated for hypertension in the context of primary care have a broader set of health issues and comorbidities than are represented within the trials that ultimately inform the clinical guidelines that guide the treatment for this population.

Limitations

While the sample is large (25,737), the study is subject to the usual potential biases associated with observational data,[233] including selection due to practice style

differences between physicians providing care to patients in this cohort.[205] We were unable to link to other databases to measure important outcomes such actual medications dispensed, acute hospital use, admission to nursing home, and death.

The validity of the comorbidity recording is a limitation of this study, a recent published study said that Canadian primary care EMR records have been found to under report, so it is possible that we do not have an accurate understanding of levels of overall health.[234] There could be appropriate patient care reasons for the trends of increased prescribing for those patients with treated SBP <120 mmHg. Similarly, without being able to link this data with actual medication dispensing information, we have used a non-specific measure of total prescriptions dispensed over a defined time period, rather than a measure of prescriptions filled or prescriptions actually taken. It is possible that the polypharmacy measure used does not reliably and consistently correlate to the number of prescriptions filled.

4.6 Conclusion

This study of >25,000 Canadians receiving hypertension treatment in primary care provides insight into the drugs used and the effects that can be observed on blood pressure, including that 9% are treated to the lowest category of systolic blood pressure, <120mmHg. This group has a significant association with being prescribed more non-hypertension medications. More research is needed to explore the possible

relationship between excessive general prescribing (polypharmacy) and possible excessive treatment of hypertension.

Chapter 5: Blood pressure treatment and incident dementia

5.1 Overview

***What is already known*:** There are mixed results about the relationship between treated blood pressure and incident dementia. In secondary analyses of hypertension trial participants, there is generally a finding of lower blood pressures being protective against cognitive decline. However, there is some observational evidence of populations more heterogeneous than trial participants that suggests an inverse relationship. This study will see if there is increased incident dementia with different levels of treated systolic blood pressure (SBP) in a sample representative of Canadians >70 years old and treated for hypertension.

***What this study adds**:*

1. This is a large heterogeneous sample of community-dwelling people being treated for hypertension. Many people in this sample have characteristics that would cause them to be excluded from the hypertension trials whose results are used to create the widely applied primary care hypertension treatment guidelines.
2. We found a significant increase in incident dementia with decreasing treated systolic and diastolic blood pressures. If this is in fact a causal relationship, being able to define a specific treatment threshold as overtreatment of hypertension in >70 years old, could reduce or delay new diagnoses of dementia. This could be translated to a recommendation to target treatment effects between an upper and

lower thresholds in clinical practice guidelines which would facilitate maximizing treatment benefit while minimizing harms.

Link to overall thesis: Treatment of asymptomatic conditions, such as hypertension have rarely been considered as inappropriate or contributing to overtreatment. These results raise real concern about the role of treating asymptomatic conditions in addressing harms of overtreatment.

5.2 Introduction

Hypertension is a widely prevalent risk factor for increased cardiovascular mortality and morbidity, and a Canadian estimate suggests 70% of people ≥ 70 years old meet diagnosis criteria.[109] Chapters 2 and 4 introduced basic background in this area, including that several randomized controlled trials (RCTs) suggest that treatment of hypertension may reduce the frequency of cardiovascular events.[100,176] Recently, the SPRINT Trial found a composite outcome of: myocardial infarction, acute coronary syndrome, stroke, acute decompensated heart failure, or death from cardiovascular causes, was decreased in the ≤120 mmHg BP target group from to 5.2% compared to 6.8% in the ≤140 mmHg BP target group, relative risk (RR) 0.76 [95% CI 0.65, 0.90], absolute risk reduction (ARR) 1.6%, number needed to treat (NNT) 63 for 3.3 years.[101] However, post hoc analysis of all serious adverse events related to the intervention showed they were increased in the low target group, 4.7% versus 2.5% in the standard BP target group, RR 1.87 [95%CI 1.50-2.33] and the Absolute Risk Increase (ARI) was 2.2%, number need to harm (NNH) 46 for 3.3. years.[235] Despite this, the 2017 Canadian

Hypertension Guidelines have included a recommendation to consider a treatment target of <120 for some people, including those >70 years old.[96] This balance between benefits and harms of treatment, especially when considering intensity of treatment, is relevant to older people with multimorbidity and/or frailty who are often not included in these trials.[201,236]

Treatment of hypertension and its relationship to incident dementia and/or worsening cognitive function are outcomes of particular interest to people over 70. Dementia is a terminal, progressive disease characterized by profound disability, poor quality of life and increased health resources use.[166] Current medical treatments for dementia are of limited utility,[83] and a more precise understanding of how hypertension treatment could prevent or ameliorate dementia would be of great use. Insight into dementia-related harms and benefits associated with various hypertension treatment thresholds that inform clinically-useful risk modification strategies could be incorporated into clinical guidelines and decision aids.

To our knowledge, there is no trial for hypertension treatment that has examined the risk of dementia as a primary outcome. However, sub-analyses of major hypertension trials have had mixed findings about the connection between hypertension treatment and dementia incidence.[89,171,237] Some observational studies of older adults have found a higher incidence of dementia[169,173] with lower blood pressure, although a definitive level at which this happens has not been identified. Mechanisms related to cerebral perfusion, where age-related vascular dysfunction and blood pressure fluctuation may

hinder sufficient perfusion for best cognitive function, have been suggested as an explanation for this apparent paradox.[238] The lack of agreement between the RCT's and observational studies could be related to flaws in observational study design. Alternatively, the difference in findings may be a reflection of the heterogeneous features of this age group that RCT exclusion criteria weeded out or were underpowered to detect.

5.1.1 Objective of this study

The objective of this study is to answer the research question: Is there an association between treated systolic or diastolic blood pressure and time to incident dementia, as observed in a pan-Canadian cohort of people ≥70 years old being treated for hypertension in primary care?

5.3 Methods

5.3.1 Study design and Sample.

This study uses a cohort design applied to data from the Canadian Primary Care Sentinel Surveillance Network (CPCSSN).[8,206] At the time of this study, CPCSSN was routinely collecting data from electronic medical records of more than 1.6 million community-dwelling patients across Canada, except Saskatchewan and the territories. Each patient record includes age, sex, CPCSSN validate diagnoses[206] (including: hypertension, diabetes, osteoarthritis, depression, dementia, epilepsy, Parkinsonism, chronic obstructive pulmonary disease (COPD)), all ICD-9 diagnostic codes associated

with primary care billing and drug prescriptions (categorized according to World Health Organization's Anatomic Therapeutic Chemical (ATC) Classification System codes[207]). A complete description of the precise ICD-9 codes, free text entries, medication prescriptions and lab results are available at the CPCSSN.ca website.[208] All patient records collected prior to June 30, 2015 were included in this study, the length of each record is different due to being included to the CPCSSN database, each patient record includes all data from the time of initial visit recorded on the electronic medical record, as opposed to the date at which CPCSSN membership was started. The project received approval from the CPCSSN research committee and ethics approval from the Providence Health Care's UBC Clinical Research Ethics Board.

5.3.2 Cohort identification criteria

The start dates for entry into the cohort were variable and Figure 5.1 describes how the baseline and observation periods were defined. We included patients who were ≥70 years at time of data collection, had a diagnosis of hypertension at any time in their health record before the start of the observation period, at least one repeated prescription for ≥1 hypertension medication and ≥3 blood pressure measures during the baseline period. Patients with a diagnosis of dementia during the baseline period were excluded. Diagnoses of hypertension and dementia were defined using the validated CPCSSN algorithms as has been presented in detail in Section 4.33 and Figure 4.3.[108,239]

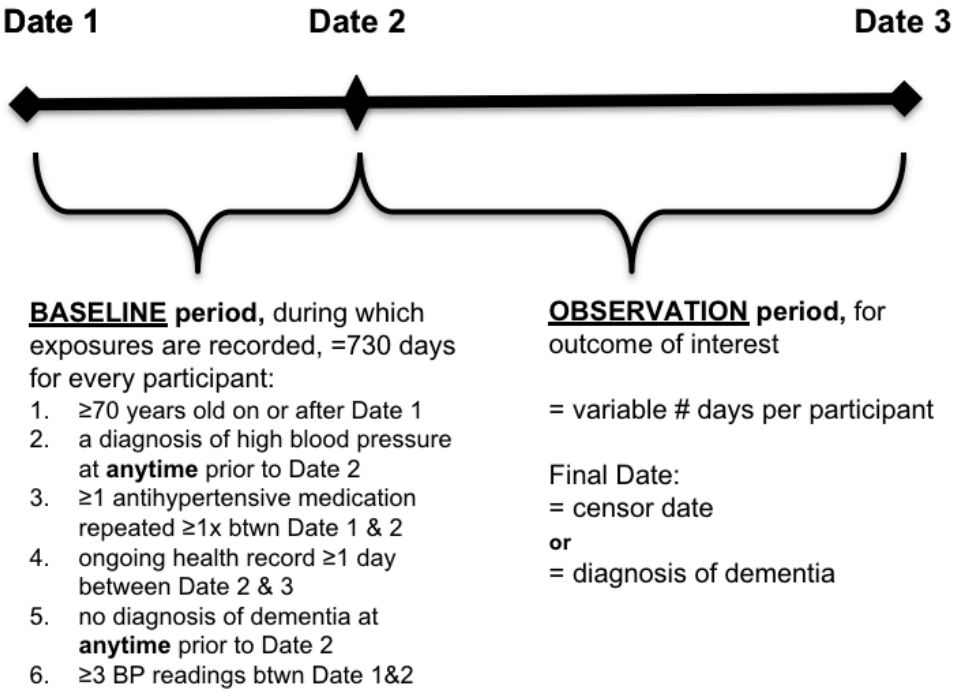


Figure 5.1 Inclusion criteria and definition of baseline and observation periods for cohort members

5.3.3 Blood pressure treatment - exposure

The independent variable is treated blood pressure and is explored to see if there are significant predictions that it can make about the dependent outcome variable, incident dementia.

Blood pressure medications

Treated blood pressure was defined using the same method described in Chapter 4 where a participant needed to have both a diagnosis of hypertension present in the record plus be prescribed ≥1 of antihypertensive during the 730-day baseline period (Figure 4.2 contains a complete list of antihypertensive drugs). Prescription information

was limited to date prescribed, agent, dose, frequency and quantity. Prescription data reports medications that were prescribed, not those that were dispensed, therefore, a repeat prescription of the same agent within the baseline period was used as a surrogate for confirmation that the prescribed medication was being dispensed and being used.

Blood pressure measurements

We calculated the mean of a minimum of three separate measures during the baseline period to address potential bias of a single reading of blood pressure, given that blood pressure is inherently variable.[240] We determined that two years was a sufficient period of time to capture most shared efforts between patient and practitioner to achieve a desired blood pressure target. Many members of the cohort will have had blood pressure treated for longer than the baseline period, but the selection of this two year period allows for collection of exposure data to be consistent for analysis of all end points, including those with the incident dementia and those censored. This period also mitigates a possible survivor bias effect.[241] There are few published studies, outside of clinical trials, about the time to effect and stability of blood pressure. The Canadian hypertension treatment guildelines[96] suggest primary care visits every 3 months to monitor blood pressure treatment, and the only available study[242] concluded that a patient-centered approach is likely to take longer than one aimed at research outcomes. No details of methods (e.g. AOBP, etc) used for capturing blood pressure measures were available in the CPCSSN dataset.

Blood pressure categories

Systolic blood pressure (SBP) is used in the main analysis as both a continuous variable and clinically meaningful categories. The majority of international hypertension guidelines recommend targeting prescription therapy below specific systolic threshold levels. Less than 120 mmHg and ≥120 mmHg were chosen to test the potential for a lower threshold at which harms may exceed benefits for hypertension therapy. There is no consensus in published medical literature on the most appropriate categories for SBP.[209] Thus, we based our 4 categories on 2017 Canadian guidelines:[96] <120, 120-139.9, 140-159.9 and ≥160 mmHg which are widely used in primary care settings in Canada.

Both low and high diastolic blood pressure (DBP)[243,244] have been implicated as a cause of dementia in previous studies, but are typically not targeted in treatment. For diastolic blood pressure, the categorical separation between ≤69 and ≥70 mmHg is based on review of observational studies describing the “j-curve” which theorizes that there is a lower threshold of blood pressure after which harms exceed benefits.[244,245]

Earlier work has suggested that the variation of SBP may have an association with dementia onset.[246,247] However, only a single trial[248] has assessed the effect of an intervention to reduce variability and to observe whether there is an effect on incident dementia. Treatment to reduce blood pressure variability is not widely performed in primary care; therefore SBP variability is included only as a baseline characteristic.

Patients were censored upon occurrence of the primary outcome (a CPCSSN dementia diagnosis), or upon reaching the last date of primary care service available in the CPCSSN data record up to and including June 30, 2015.

5.3.4 Diagnosis of Dementia - Outcome

Diagnosis of dementia was recorded as the first date on which any of the conditions of the CPCSSN algorithm for dementia were met. The CPCSSN definition of dementia includes both a range of ICD9 codes as well as ATC codes for dementia specific medications (cholinesterase inhibitors) and has been found to have a sensitivity of 96.8% (95%CI 93.3-100) and specificity of 98.1 (95%CI 97.5%-98.7%).[206,208,239]

5.3.5 Baseline measures of potential confounding factors

To address the potential for confounding by other factors, we reviewed the literature and, a priori, selected covariates that have been previously studied and shown to have plausible associations with the risk for incident dementia.[249–251] These included baseline measures of:

1. age,
2. sex,
3. presence of these diagnoses at any time in the record prior to end of baseline period (Figure 5.1):
    a. congestive heart failure
        i. ICD9=428 or prescription of furosemide[188]
    b. other cardiovascular disease
        i. see Figure 4.3 for detailed description, includes: ICD9 codes, 410, 411, 412, 413, 414, 427, 441.4, 441.3, 441.9, 441.01, 443.9 or 440.21
    c. cerebrovascular disease
        i. ICD9 codes430, 431, 432, 433, 434, 435, 436, 437, 438 or V12.54

    d. diabetes
        i. CPCSSN algorithm[206]
    e. depression
        i. CPCSSN algorithm[206]
    f. Parkinson's disease
        i. CPCSSN algorithm[206]

4. **Exposure to anticholinergic medication**, which has been found to affect cognition:[251] counted as present if found to have a repeated prescription of an anticholinergic medication (complete list in Figure 5.2) within the baseline period;

5. **Measure of concurrent burden of illness**, where increased health instability has been found to be associated with earlier diagnosis of dementia.[252] A validated measure of co-morbidity was not available using CPCSSN data, so the following 4 variables were used as a surrogate:
    a. Health record changes: the total number of changes made to the medical record during the baseline period; and
    b. Polypharmacy:[85] the number of prescriptions written during the baseline period.
    c. Variability in systolic blood pressure measures,[253] where increased variation is associated with higher risk of dementia.
    d. Having at least 3 co-morbidities, in addition to hypertension.[252]

Diagnoses were considered present if reported at any time prior to or during the baseline period. The sum of changes to the health record, prescriptions written, variability in systolic blood pressure, and sum of co-morbidities were used as a surrogate measure of overall burden of illness[254] since calculation of a standardized measure of co-morbidity (e.g. the Charlson Comorbidity Index),[222] was not possible within the CPCSSN dataset. Changes to the health record include: visits to primary care, notes added by other team members, results from lab tests being added, etc, a larger number of changes are assumed to be associated with a higher level of co-morbidity.[255,256]

Anticholinergic Medications

World Health Organization Anatomic Therapeutic Chemical (ATC) code, name

Categories from Anticholinergic section of 2015 American Geriatrics Society Updated Beers Criteria.

Skeletal Muscle Relaxants
M03BX08 cyclobenzaprine
N04AB02 orphenadrine (chloride)

Antiarrythmic
C01BA03 disopyramide

Antihistamines
R06AB01 brompheniramine
R06AA08 carbinoxamine
R06AB04 chlorphenamine
R06AA04 clemastine
R06AX02 cyproheptadine
R06AB02 dexchlorpheniramine
R06AA02 diphenhydramine
R06AA52 diphenhydramine, comb.
R06AA09 doxylamine
N05BB01 hydroxyzine
R06AE05 meclozine
R06AX07 triprolidine

Antidepressants
N06AA09 amitriptyline
N06AA04 clomipramine
N06AA01 desipramine
N06AA12 doxepin
N06AA02 imipramine
N06AA03 imipramine oxide
N06AA10 nortriptyline
N06AA11 protriptyline
N06AA06 trimipramine
N06AB05 paroxetine

Antiparkinsonian agents
N04AA01 trihexyphenidyl
N04AC01 benzatropine

Antimuscarinics
G04BD10 darifenacin
G04BD11 fesoterodine
G04BD02 flavoxate
G04BD04 oxybutynin
G04BD08 solifenacin
G04BD07 tolterodine
G04BD09 trospium

Antipsychotics
N05AA01 chlorpromazine
N05AH02 clozapine
N05AH01 loxapine
N05AH03 olanzapine
N05AB03 perphenazine
N05AC02 thioridazine
N05AB06 trifluoperazine

Antispasmodics
A03BA01 atropine
A03BA03 hyoscyamine
A03BA04 belladonna tot. alkaloids
A03AB05 propantheline
S01FA05 homatropine
S01FA02 scopolamine
N05BA02 chlordiazepoxide
A03AA07 dicyclomine

Anti-emetic
N05AB04 prochlorperazine
R06AD02 promethazine

Figure 5.2 List of included anticholinergic medications

5.3.6 Statistical Analysis

Patient characteristics are presented in groups according to the mean SBP in the baseline period. Statistical differences between the groups were examined using t-tests, chi-squared and Kruskal Wallis tests, where appropriate. The hazard ratio for risk of incident dementia associated with an increase or decrease in blood pressure was measured with a Cox proportional hazards model and is presented with 95% confidence intervals. The Cox model was selected for its ability to investigate the relationship of multiple predictors and the time to event calculated by the hazard function, in addition to the typical inclusion of censored data, that is provided through all survival functions.[257] Hazard ratios (HR) that are greater than zero indicate a variable to indicate an increased risk, and inversely, a HR less than zero identifies a protective factor.

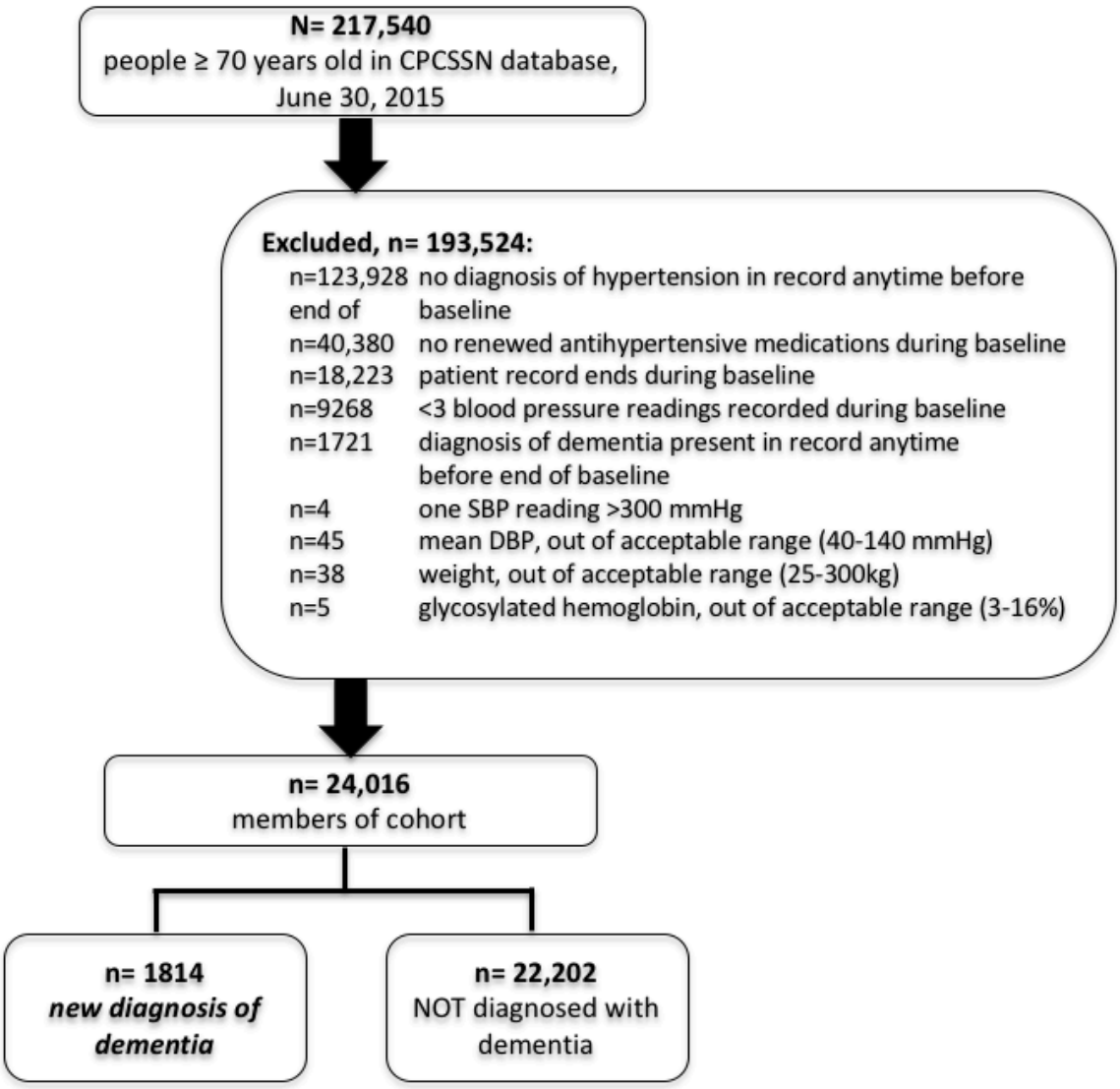
The Cox model was used with DBP and SBP as both a continuous (per 1 mmHg) and two types of categorical variables (binary and four categories) to allow for maximal comparison with previous work in this area. We identified several covariates a priori based on previously studied associations with incident dementia, including: age, sex, congestive heart failure, ischemic heart disease, cerebrovascular disease (including stroke), Parkinson's disease, depression, diabetes, repeated anticholinergic prescription, burden of illness. A sensitivity analysis was done (by repeating the analysis with removal of the variable ≥3 co-morbidities) to observe possible collinearity between presence of single diseases and a categorical measure of ≥3 co-morbidities which was derived from the sum of all individual co-morbidities.

The proportional hazards assumption was tested using the Kaplan Meier method and Schoenfeld residuals.[258] A p-value of 0.05% was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics for Mac, Version 24.0. Armonk, NY: IBM Corp.

5.4 Results

5.4.1 Demographics

Of the 24016 eligible cohort members, 1814 (7.6%) were diagnosed with dementia during the observation period. Figure 5.3 provides details of cohort exclusion for medication, measurement, or record length/quality requirements.



hypertension = High blood pressure, as per CPCSSN algorithm
hypertension medications = angiotensin-converting enzyme inhibitors, calcium channel blockers, thiazide-like diuretics, β-blockers, angiotensin II type 1 receptor antagonists, spironolactone, furosemide & α-adrenergic blocking agents, nitrates

Figure 5.3 Members of cohort, flow diagram

The length of the observation period varied between 1 and 4327 days with a median of 898 days (IQR 433, 1581). Median number of days from the start of the observation period (Date 2) to time of dementia was 784 days (IQR 345, 1464) time in cohort). Mean age at time of diagnosis of dementia was 90.1 years (SD ±6.7, IQR 86.3, 95.6).

Table 5.1 provides a description of the cohort, by systolic blood pressure categories. Distributed in the SBP categories as follows: <120 mmHg, 8.6%, 120-139.9 mmHg, 56.7%, 140-159.9 mmHg 30.8% and >160 mmHg, 3.9% and were found to have significant differences for almost all characteristics observed. Those with SBP <120 mmHg had more co-morbidities, including higher frequencies of depression,16.8%, diabetes, 32.2%, chronic obstructive pulmonary disease (COPD) 19.5%, congestive heart failure (CHF), 34.5%, cardiovascular disease, 34.5% and cerebrovascular disease, 4.7%. This group, also had the fewest women, 47.8% and the shortest observation period, 2.1 years, versus 2.4-2.8 years for the other categories.

Table 5.1 Characteristics of cohort members, by systolic blood pressure (mmHg) categories

	SBP <120	SBP 120-139	SBP 140-159	SBP 160
Participant count, n (%)	2064 (8.6)	13,613(56.7)	7,395 (30.8)	944 (3.9)
age, mean ±SD	82.4 ±6.7	81.7 ±6.5	82.5 ±6.6	83.8 ±6.9
Female sex	987(47.8)	8051(59.1)	4885(66.1)	685 (72.6)
female weight (kg) n=12,870	72.4 ±23.0	73.7 ±22.9	73.8 ±23.0	71.2 ±22.6
male weight (kg) n=8465	86.2 ±23.8	89.0 ±24.3	88.7 ±24.6	86.9 ±24.4
Years observed*, median, (IQR)	2.12 (0.98, 3.89)	2.41(1.18-4.23)	2.66(1.25-4.61)	2.75(1.32-4.74)
Smoking#, current or past, n=3402	350 (17.0)	1921 (14.1)	1008(13.6)	123 (13.0)
Low density cholesterol (LDL), median, (IQR) n =19731	2.0 (1.5,2.6)	2.3 (1.7,2.9)	2.6 (1.9,3.2)	2.7 (2.0,3.5)
Glycosylated hemoglobin (A1c), % median (IQR) n =16374	6.0 (5.7,6.5)	6.0 (5.7, 6.5)	6.0 (5.7, 6.4)	5.9 (5.7,6.5)
PRESCRIBING				
# prescriptions, mean ±SD	11.2 ±5.7	9.6 ±5.4	9.2 ±5.3	8.8 ±4.9
# renewed hypertension medications, median, (IQR)	2 (1,3)	2 (1,3)	2 (1,3)	2 (1,3)
anticholinergic drug, n (%)	281 (13.6)	1682(12.4)	815 (11.0)	80 (8.5)
CONCURRENT COMORBIDITIES				
depression, n (%)	346 (16.8%)	1781(13.1%)	790 (8.6%)	81 (8.6%)
diabetes, n (%)	664 (32.2%)	3761(27.6%)	1828(24.7%)	244 (25.8%)
chronic obstructive pulmonary disease, n (%)	403 (19.5%)	1755(12.9%)	802(10.8%)	80 (8.5%)
osteoarthritis, n (%)	613 (29.7%)	4035 (29.6%)	2215(30.0%)	227 (24.0%)
congestive heart failure(CHF), n (%)	553 (26.8%)	1855 (13.6%)	874 (11.8%)	115 (12.2%)
other cardiovascular disease n (%) (not including CHF)	713 (34.5%)	2977(21.9%)	1202(16.3%)	125 (13.2%)
cerebrovascular disease, n (%) (including stroke)	97 (4.7%)	604 (4.4%)	252 (3.4%)	24 (2.5%)
Parkinson's disease, n (%)	30 (1.5%)	126 (0.9%)	58 (0.8%)	6 (0.6%)
epilepsy, n (%)	30 (1.5%)	150 (1.1%)	60 (0.8%)	12 (1.3%)
BURDEN OF ILLNESS & BP MEASURES				
# health record changes, median, (IQR)	24 (16,36)	21 (14,32)	21 (14,30)	19 (13,28)
hypertension + ≥3 co-morbidities, n (%)	688 (33.3%)	2796 (20.5%)	1176 (15.9%)	118 (12.5%)
Co-efficient of variation for SBP, mean ±SD	0.09 ±0.04	0.08 ±0.04	0.09 ±0.04	0.10 ±0.09
diastolic blood pressure, mmHg, mean ±SD	67.0 ±6.4	72.9 ±6.8	76.4 ±7.8	81.3 ±9.5
pulse pressure, mean ±SD	47.2 ±6.7	58.2 ±7.7	70.7 ±8.9	87.1 ±11.2
# BP readings, median, (IQR)	7 (5,11)	7 (5,11)	8 (5,12)	7 (4,11)

** Observation period starts 731 days after the start of the baseline period, observation ends on the date of the event of interest (dementia diagnosis) or at the last recorded office visit, Reference Figure 5.1.*
 # Smoking data missing for 16,422 members of cohort
SD = standard deviation; BP = blood pressure; IQR = interquartile range

5.4.2 Associations between blood pressure treatment and incident dementia

Blood pressure as continuous variable in the adjusted model

The Cox proportional hazards model assessed the possible association between SBP and DBP and incident dementia. Using blood pressure as a continuous variable in our Cox model, we found a significant decreased risk of dementia for every 1 mmHg increase in SBP, hazard ratio (HR) 0.991 (95%CI 0.987-0.995, p = <.0001). Similarly, for DBP, there was a decreased risk with every 1 mmHg increase, HR 0.989 (95%CI 0.983-0.995 p = <.0001). Tables 5.2 and 5.3 present the details of the Cox proportional hazard model results for both SBP and DBP.

Blood pressure as categorical variable

When we examined the association between binary categories of SBP and incident dementia in our adjusted Cox proportional hazards model, we found having a SBP <120 mmHg (versus ≥120 mmHg) had a HR 1.278 (95% CI 1.089 -1.500, p=0.003) for risk of incident dementia. Similarly, DBP <70 mmHg (versus ≥70 mmHg) has a HR of 1.229 (95% CI 1.111-1.360, p = <.0001) for increased risk of incident dementia. The proportional hazards assumption was maintained for the models with 2 categories of SBP and DBP as demonstrated by the Kaplan Meier survival curves in Figures 5.4 - 5.7.

To evaluate the associations with additional categories of SBP, we used 120-139.9 mmHg as the reference range and applied the adjusted model. We found <120mmHg HR 1.179 (95%CI 1.001-1.389 p=0.049), 140-159 mmHg HR 0.813 (95%CI 0.732-0.903

p= <0.0001) ≥160 mmHg HR 0.760 (95%CI 0.593-0.974 p=0.030). In this model, there is concern about the maintenance of the proportional hazards assumption as the top lines (≥160 mmHg) of the Kaplan Meier curve crossed (Figure 5.5). This category also has the smallest number of cohort members and therefore predictably shows the greatest variability over time.[259]

Sensitivity Analysis for ≥3 co-morbidities

Tables 5.4 and 5.5 show the entire Cox model for both SBP and DBP repeated with removal of the variable ≥3 co-morbidities. The effect on hazard ratios for various presentations of blood pressure is minimal. However, the hazard ratios for the specific diseases listed are affected. Specifically, in the original model, the inclusion of ≥3 co-morbidities suggests either collinearity between the single disease and the summary variables or a protective effect of single diagnoses, except Parkinson's disease. The answer is most likely collinearity as the sensitivity analysis removes the apparent "protective effect" of some diagnoses and shows a more expected pattern of increased risk, in particular for cerebrovascular disease, depression, and Parkinson's.

Figure 5.2 shows all measures of SBP have a significant result but that ≥3 co-morbidities is the only measure of burden of illness (composed of: # health record changes, # of prescriptions, SBP variability) that is significant with a HR 8.125 (95%CI 7.011-9.416, p<.001) . In Figure 5.4, SBP variability is not significant, but # of health record changes and # of prescriptions have a small but statistically significant result.

Table 5.2 Cox proportional hazards model, systolic blood pressure

	SBP, per 1mmHg				SBP, < or ≥120 mmHg				SBP, 4 categories			
			95% CI				95% CI				95% CI	
	p	HR	Upper	Lower	p	HR	Upper	Lower	p	HR	Upper	Lower
SBP per 1mmHg	**0.000**	**0.991**	**0.987**	**0.995**	-	-	-	-	-	-	-	-
SBP <120 mmHg	-	-	-	-	**0.003**	**1.278**	**1.089**	**1.500**	**0.049**	**1.179**	**1.001**	**1.389**
SBP 120-139.9 mmHg	-	-	-	-	-	-	-	-	*reference*			
SBP 140-159.9 mmHg	-	-	-	-	-	-	-	-	**0.000**	**0.813**	**0.732**	**0.903**
SBP >160mmHg	-	-	-	-	-	-	-	-	**0.030**	**0.760**	**0.593**	**0.974**
Characteristics and burden of illness												
male sex	0.812	0.988	0.894	1.091	0.623	0.975	0.883	1.077	**0.000**	**1.078**	**1.070**	**1.086**
age	**0.000**	**1.078**	**1.071**	**1.086**	**0.000**	**1.077**	**1.069**	**1.085**	0.797	0.987	0.893	1.090
# of health record changes	0.928	1.000	0.997	1.003	0.828	1.000	0.997	1.004	0.953	1.000	0.997	1.003
# of prescriptions	0.441	1.004	0.993	1.015	0.417	1.005	0.994	1.016	0.420	1.005	0.994	1.016
SBP variability	0.203	2.096	0.672	6.542	0.481	1.494	0.489	4.571	0.226	1.979	0.656	5.971
hypertension + ≥3 co-morbidities	**0.000**	**8.125**	**7.011**	**9.416**	**0.000**	**8.102**	**6.992**	**9.388**	**0.000**	**8.130**	**7.016**	**9.421**
anticholinergic prescription	**0.000**	**1.254**	**1.113**	**1.413**	**0.000**	**1.255**	**1.114**	**1.415**	**0.000**	**1.257**	**1.116**	**1.416**
Specific co-morbidities												
congestive heart failure	**0.000**	**0.466**	**0.403**	**0.540**	**0.000**	**0.471**	**0.407**	**0.545**	**0.000**	**0.468**	**0.404**	**0.542**
cerebrovascular disease (incl. stroke)	**0.000**	**0.611**	**0.496**	**0.753**	**0.000**	**0.618**	**0.502**	**0.762**	**0.000**	**0.612**	**0.496**	**0.754**
other cardiovascular disease	**0.000**	**0.319**	**0.276**	**0.368**	**0.000**	**0.324**	**0.281**	**0.373**	**0.000**	**0.319**	**0.277**	**0.368**
diabetes	**0.000**	**0.671**	**0.596**	**0.755**	**0.000**	**0.676**	**0.601**	**0.760**	**0.000**	**0.673**	**0.598**	**0.757**
depression	**0.000**	**0.678**	**0.585**	**0.785**	**0.000**	**0.689**	**0.596**	**0.798**	**0.000**	**0.678**	**0.585**	**0.785**
Parkinson's disease	**0.004**	**1.607**	**1.164**	**2.218**	**0.005**	**1.591**	**1.153**	**2.197**	**0.004**	**1.609**	**1.165**	**2.221**

Table 5.3 Cox proportional hazards model, diastolic blood pressure

	DBP, per 1mmHg				DBP, < or ≥70 mmHg				DBP, 4 categories			
			95% CI				95% CI				95% CI	
	p	HR	Upper	Lower	p	HR	Upper	Lower	p	HR	Upper	Lower
DBP per 1mmHg	**0.000**	**0.987**	**0.981**	**0.993**	-	-	-	-	-	-	-	-
DBP <70 mmHg	-	-	-	-	**0.000**	**1.229**	**1.111**	**1.360**	**0.001**	**1.195**	**1.075**	**1.329**
DBP 70-79.9 mmHg	-	-	-	-	-	-	-	-	reference			
DBP 80-89.9 mmHg	-	-	-	-	-	-	-	-	0.139	0.906	0.794	1.033
SBP >90mmHg	-	-	-	-	-	-	-	-	0.343	0.830	0.565	1.220
Characteristics and burden of illness												
male sex	0.499	0.966	0.875	1.067	0.514	0.967	0.876	1.068	0.500	0.966	0.875	1.067
age	**0.000**	**1.075**	**1.067**	**1.083**	**0.000**	**1.075**	**1.067**	**1.083**	**0.000**	**1.075**	**1.067**	**1.083**
# health record changes	0.841	1.000	0.997	1.004	0.782	1.000	0.997	1.004	0.820	1.000	0.997	1.004
# of prescriptions	0.578	1.003	0.992	1.014	0.528	1.004	0.993	1.015	0.577	1.003	0.992	1.014
SBP variability	0.445	1.541	0.508	4.671	0.543	1.417	0.461	4.355	0.480	1.495	0.489	4.568
hypertension + ≥3 co-morbidities	**0.000**	**8.152**	**7.035**	**9.446**	**0.000**	**8.181**	**7.060**	**9.481**	**0.000**	**8.169**	**7.049**	**9.466**
anticholinergic drug	**0.000**	**1.265**	**1.122**	**1.425**	**0.000**	**1.264**	**1.122**	**1.424**	**0.000**	**1.262**	**1.120**	**1.422**
Specific co-morbidities												
congestive heart failure	**0.000**	**0.470**	**0.406**	**0.544**	**0.000**	**0.469**	**0.405**	**0.543**	**0.000**	**0.469**	**0.405**	**0.543**
cerebrovascular disease (incl. stroke)	**0.000**	**0.615**	**0.499**	**0.758**	**0.000**	**0.621**	**0.504**	**0.765**	**0.000**	**0.619**	**0.503**	**0.763**
other cardiovascular disease	**0.000**	**0.323**	**0.280**	**0.373**	**0.000**	**0.323**	**0.280**	**0.373**	**0.000**	**0.323**	**0.280**	**0.373**
diabetes	**0.000**	**0.658**	**0.584**	**0.740**	**0.000**	**0.660**	**0.586**	**0.743**	**0.000**	**0.657**	**0.583**	**0.739**
depression	**0.000**	**0.694**	**0.600**	**0.803**	**0.000**	**0.695**	**0.601**	**0.804**	**0.000**	**0.695**	**0.601**	**0.804**
Parkinson's disease	**0.003**	**1.635**	**1.184**	**2.257**	**0.004**	**1.604**	**1.162**	**2.214**	**0.003**	**1.623**	**1.175**	**2.241**

Table 5.4 Cox model, systolic blood pressure, ≥3 co-morbidities removed

	SBP, per 1mmHg				SBP, < or ≥120 mmHg				SBP, 4 categories			
			95% CI				95% CI				95% CI	
	p	HR	Upper	Lower	p	HR	Upper	Lower	p	HR	Upper	Lower
SBP per 1mmHg	**0.000**	**0.991**	**0.988**	**0.995**	-	-	-	-	-	-	-	-
SBP <120 mmHg	-	-	-	-	**0.002**	**1.289**	**1.098**	**1.513**	**0.029**	**1.200**	**1.019**	**1.414**
SBP 120-139.9 mmHg	-	-	-	-	-	-	-	-	reference			
SBP 140-159.9 mmHg	-	-	-	-	-	-	-	-	**0.001**	**0.837**	**0.754**	**0.930**
SBP >160mmHg	-	-	-	-	-	-	-	-	**0.013**	**0.731**	**0.570**	**0.937**
Characteristics and burden of illness												
male sex	0.940	0.996	0.901	1.101	0.741	0.983	0.890	1.086	**0.000**	**1.079**	**1.071**	**1.087**
age	**0.000**	**1.079**	**1.071**	**1.087**	**0.000**	**1.078**	**1.070**	**1.086**	0.921	0.995	0.900	1.100
# of health record changes	**0.033**	**1.003**	**1.000**	**1.007**	**0.026**	**1.004**	**1.000**	**1.007**	**0.035**	**1.003**	**1.000**	**1.007**
# of prescriptions	**0.040**	**1.012**	**1.001**	**1.023**	**0.032**	**1.012**	**1.001**	**1.023**	**0.037**	**1.012**	**1.001**	**1.023**
SBP variability	0.366	1.678	0.546	5.157	0.773	1.176	0.391	3.538	0.429	1.556	0.521	4.645
anticholinergic prescription	**0.000**	**1.267**	**1.124**	**1.429**	**0.000**	**1.273**	**1.129**	**1.435**	**0.000**	**1.268**	**1.125**	**1.430**
Specific co-morbidities												
congestive heart failure	0.097	0.889	0.774	1.022	0.122	0.896	0.780	1.030	0.104	0.891	0.775	1.024
cerebrovascular disease (incl. stroke)	**0.006**	**1.326**	**1.085**	**1.620**	**0.005**	**1.335**	**1.092**	**1.631**	**0.006**	**1.327**	**1.086**	**1.622**
other cardiovascular disease	0.423	0.953	0.847	1.072	0.536	0.964	0.856	1.084	0.421	0.953	0.847	1.072
diabetes	0.160	1.082	0.969	1.207	0.140	1.086	0.973	1.212	0.161	1.082	0.969	1.207
depression	**0.002**	**1.245**	**1.086**	**1.427**	**0.001**	**1.256**	**1.095**	**1.439**	**0.002**	**1.246**	**1.086**	**1.428**
Parkinson's disease	**0.000**	**2.897**	**2.108**	**3.983**	**0.000**	**2.860**	**2.081**	**3.932**	**0.000**	**2.890**	**2.102**	**3.973**

Table 5.5 Cox model, diastolic blood pressure, ≥3 co-morbidities removed

	DBP, per 1mmHg				DBP, < or ≥70 mmHg				DBP, 4 categories			
			95% CI				95% CI				95% CI	
	p	HR	Upper	Lower	p	HR	Upper	Lower	p	HR	Upper	Lower
DBP per 1mmHg	**0.000**	**0.989**	**0.983**	**0.995**	-	-	-	-	-	-	-	-
DBP <70 mmHg	-	-	-	-	**0.002**	**1.172**	**1.059**	**1.296**	**0.016**	**1.139**	**1.025**	**1.267**
DBP 70-79.9 mmHg	-	-	-	-	-	-	-	-	reference			
DBP 80-89.9 mmHg	-	-	-	-	-	-	-	-	0.148	0.908	0.797	1.035
SBP >90mmHg	-	-	-	-	-	-	-	-	0.282	0.81	0.551	1.189
Characteristics and burden of illness												
male sex	0.591	0.973	0.881	1.075	0.600	0.974	0.881	1.076	0.584	0.973	0.880	1.074
age	**0.000**	**1.076**	**1.068**	**1.084**	**0.000**	**1.077**	**1.069**	**1.084**	**0.000**	**1.076**	**1.068**	**1.084**
# of health record changes	**0.026**	**1.004**	**1.000**	**1.007**	**0.024**	**1.004**	**1.000**	**1.007**	**0.027**	**1.004**	**1.000**	**1.007**
# of prescriptions	**0.049**	**1.011**	**1.000**	**1.022**	**0.037**	**1.012**	**1.001**	**1.023**	**0.046**	**1.011**	**1.000**	**1.022**
SBP variability	0.746	1.198	0.402	3.571	0.823	1.134	0.376	3.416	0.758	1.188	0.397	3.557
anticholinergic prescription	**0.000**	**1.285**	**1.140**	**1.450**	**0.000**	**1.281**	**1.136**	**1.444**	**0.000**	**1.281**	**1.136**	**1.445**
Specific co-morbidities												
congestive heart failure	0.122	0.896	0.780	1.030	0.123	0.896	0.780	1.030	0.124	0.897	0.780	1.030
cerebrovascular disease (incl. stroke)	**0.005**	**1.335**	**1.093**	**1.631**	**0.004**	**1.344**	**1.100**	**1.642**	**0.004**	**1.338**	**1.095**	**1.635**
other cardiovascular disease	0.588	0.968	0.861	1.089	0.618	0.970	0.863	1.092	0.598	0.969	0.861	1.090
diabetes	0.289	1.062	0.951	1.186	0.251	1.067	0.955	1.191	0.289	1.062	0.950	1.186
depression	**0.001**	**1.263**	**1.102**	**1.448**	**0.001**	**1.264**	**1.102**	**1.449**	**0.001**	**1.264**	**1.102**	**1.449**
Parkinson's disease	**0.000**	**2.930**	**2.131**	**4.029**	**0.000**	**2.886**	**2.099**	**3.967**	**0.000**	**2.915**	**2.120**	**4.010**

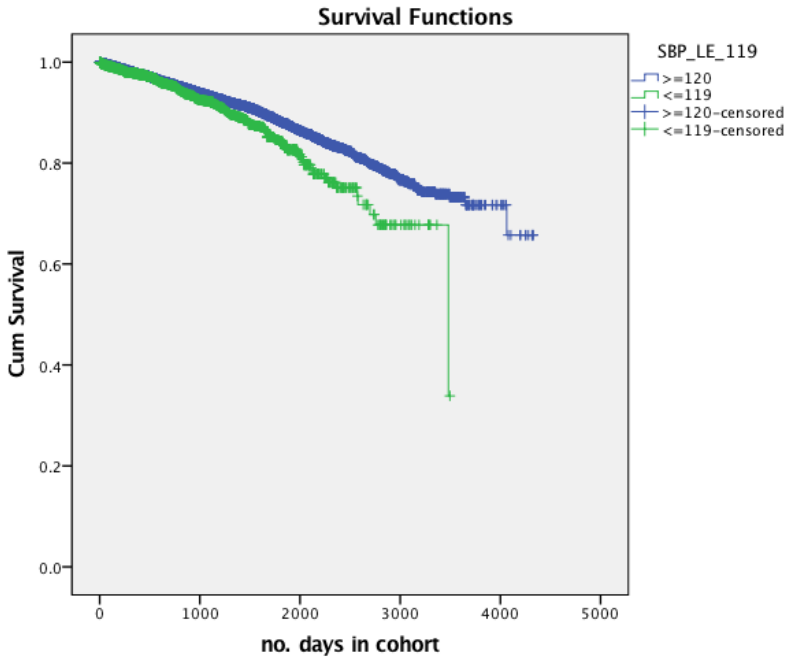


Figure 5.4 Kaplan Meier survival curve: systolic blood pressure, 2 categories

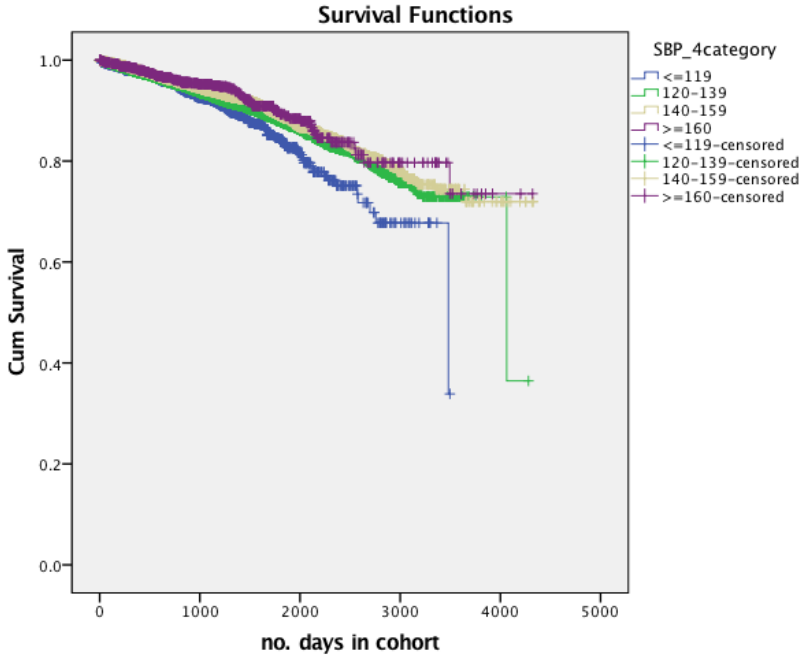


Figure 5.5 Kaplan Meier survival curve: systolic blood pressure, 4 categories

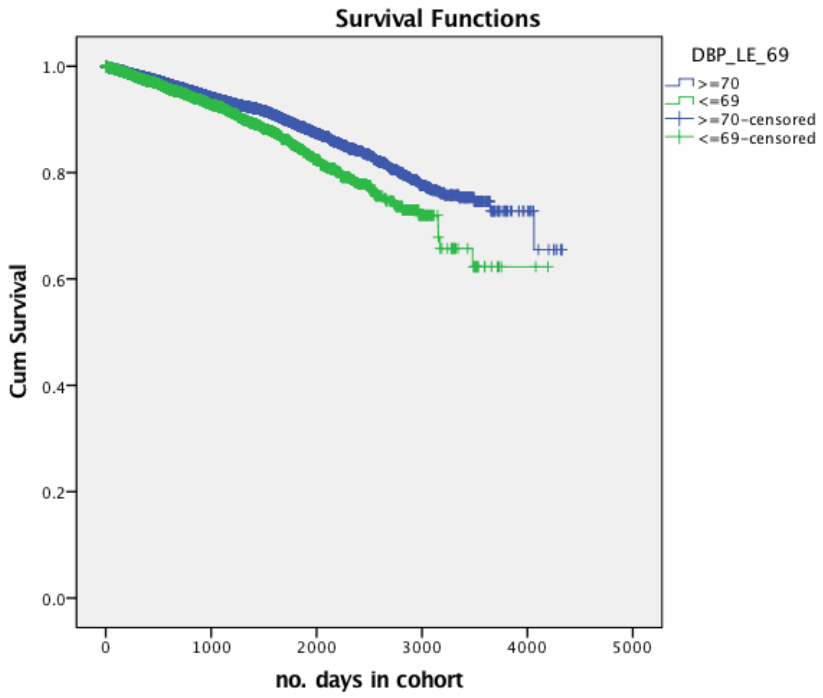


Figure 5.6 Kaplan Meier survival curve, diastolic blood pressure, 2 categories

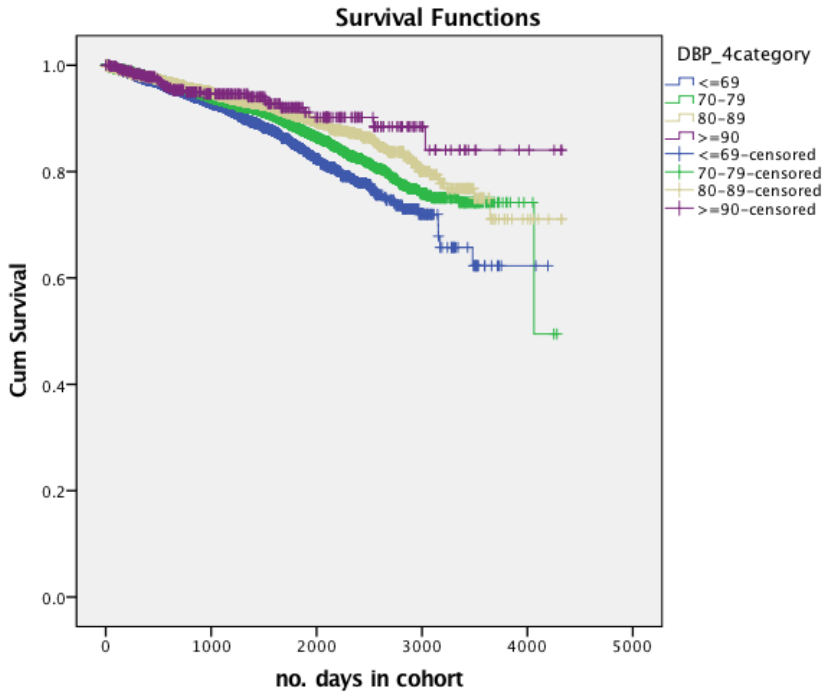


Figure 5.7 Kaplan Meier survival curve, diastolic blood pressure, 4 categories

5.5 Discussion

In this single study of 24,016 community-dwelling Canadians, ≥70 years old, and being treated for hypertension, we found an association between lower systolic and diastolic blood pressure and increased risk of incident dementia. The association persisted when we assessed blood pressure as both a continuous variable (reported per 1 mmHg), and as a binary category and as 4 categories. Significant comorbidity, where a cohort member has ≥3 co-morbidities, in addition to hypertension was found to be most predictive of an increased risk of incident dementia, other measures of burden of illness were inconsistently predictive. However, despite this fluctuation, the sensitivity analyses still found the blood pressure risks for incident dementia remained almost the same and statistically significant. Risk of incident dementia is increased with lower blood pressure and risk is reduced with higher blood pressure. Greater than three co-morbidities is also significantly associated with increased risk of dementia.

Other longitudinal studies examining the link between blood pressure and incident dementia have had mixed results, particularly for systolic blood pressure. In 2015, Mossello et al[191] studied blood pressure treatment in a cohort of 193 cognitively impaired community dwelling people ≥65 years old (Mini Mental Status Exam (MMSE), mean score 22.1 (SD 4.4), range 10-27)). They found that those people treated with antihypertensive drugs, to a daytime SBP <=128 mmHg, had a faster cognitive decline that those with SBP 129-144 or >145 mmHg over 6-18 months (<=128 mmHg mean MMSE score change -3.9 (SD 3.5) versus 129-144 mmHg -0.6 (SD 2.2) and ≥145

mmHg -0.4 (SD 3.7)). Our results are also similar to those found in the 2011 meta-analysis by Power et al (2011) who reported a summary estimate of HR 0.95 (95% CI 0.91-1.00) for each 10mmHg increase of SBP and HR 0.94 (95% CI 0.85-1.04) for each 10mmHg increase of DBP.[169]

In a 2009 Cochrane review, McGuinness et al combined the results of 4 hypertension trials (SHEP 1991,[177] Syst Eur 1997,[260] SCOPE 2003,[179] HYVET 2008[90]) that compared active hypertensive treatment to placebo and that had dementia as a secondary outcome.[171] Their meta-analysis, whose participants had a mean age 75.4 years and were subject to the exclusion criteria of the reviewed trials, found no difference between placebo and treatment groups for incidence of dementia, OR 0.89 (95%CI 0.74, 1.07) (favoring treatment). The authors concluded that they could not estimate the optimal blood pressure for dementia prevention. Mean blood pressure at entry was 171/86 mmHg with an end of trial SBP of (weighted mean difference) -10.22 mmHg (95%CI -10.78 to -9.66). Previous studies have suggested that age-related atherosclerosis and consequent cerebral hypo-perfusion may explain why some studies have found the inverse relationship.[243] However, despite review and study, the exact physiological explanation has not yet been determined.[261]

In contrast to our findings, a recent study looking at potential racial differences in hypertension mortality and morbidity by Hajjar et al[262] reported that there was a protective effect on long term cognitive trajectories for older people with lower blood pressure. Repeated measures of the Modified Mini Mental State Exam (3MSE) and

Digit Symbol Substitution Test (DSST), over 10 years, were used to track cognitive trajectories. Specifically, they found that the decreases in 3MSE was 3.7 when SBP ≥150 mmHg (P<.001) and 3.0 if SBP <120 mmHg. However, while the difference was statistically different, clinically meaningful differences in the 3MSE have been validated as ≥5.0.[263,264] The cohort was drawn from the Healthy Aging and Body Composition Study, which collected data between 1997-2007 from well-functioning, cognitively intact participants age 70-79. The sample raised concerns about attrition bias when compared to a representative community-dwelling sample that we were able to access.[265]

While our study does not provide information regarding causality, our results allow hypothesis generation about the potential benefits of prescribing or discontinuing antihypertensives to treat blood pressure between both an upper and lower threshold. Our study looked only at those receiving blood pressure lowering medications. The Dante trial[266] looked at nursing home dwelling participants who already had dementia and were being treated for hypertension with a blood pressure below 140 mmHg. The intervention was to reduce treatment to permit a higher systolic pressure (up to 160 mmHg) in an effort to improve cognition. After 16 weeks, there was no difference in cognition between groups, but there was also no increase in cardiovascular events. A recent review of this topic[168] found only two studies and found insufficient evidence to make recommendations about the safety or utility of antihypertensive withdrawal.

Limitations

There are important limitations of this study that should factor into the interpretation of results. This study is a secondary analysis of data routinely collected in clinical encounters. The study design was limited to the information that was available within the record and what could be standardized for analysis. This has particular importance related to the two diseases of interest, dementia and hypertension. To identify incident dementia, we needed to rely on a diagnosis code or prescription of a dementia-related medication. Without having a specific measure of cognitive function, it is impossible to know at what point in the disease trajectory these codes or medications started being used. If diagnoses and prescriptions are being recorded in the medical record at later stages of dementia, people with earlier dementia symptoms that will progress are not reported in this cohort. This could translate to an under- or over-report of incident cases for any level of SBP or DBP. However, the sensitivity and specificity of our dementia-identifying algorithm[206] gives confidence that the cases we are describing are most likely true diagnoses.

Similarly, we were not able to include information about midlife hypertension history and treatment. Previous studies have found that midlife (age 44-66 years) hypertension (SBP ≥140 mmHg) has been associated with increased risk for dementia, e.g. Gottesman et al, HR 1.39 (95% CI 1.22-1.59).[267] It would have been ideal to compare length of diagnosis of hypertension with incident dementia when over age 70 to see if there was a difference between those whose BP had been high in mid-life, versus those whose diagnosis was newer. Neither did we have accurate information about

medication switching and we were unable to link to other sources of data which would have allowed a more robust picture of medications actually dispensed, visits to specialty care, admissions to nursing homes or hospitals, and deaths.

Those with a SBP of 120 mmHg (n= 2064) appear to have higher rates of most co-morbidities when compared with individuals in other SBP categories. They also have a significantly shorter time in the observation period (2.12 years (IQR 0.98-3.89) versus the e.g. ≥160 mmHg category (2.75 (IQR 1.32-4.74)). This may be due to both earlier deaths and leaving the cohort due to admission to a nursing home facility and could support alternate explanations, such as a higher burden of illness, rather than low SBP/DBP, as the cause for increased hazard for incident dementia.

Interpretation

Routine prescription of antihypertensive medications to lower blood pressure, particularly <120mmHg systolic or <70 mmHg diastolic, may have an increased risk for an earlier diagnosis of dementia. We found that higher treated SBP and DBP are both associated with decreased hazard of dementia. The risk was small, but significant even when co-morbidity was considered. This suggests that it may be possible to either ameliorate risk or delay onset of incident dementia, even in those people with ≥3 co-morbidities.

Current clinical practice guidelines do not include information about risks of lower blood pressure nor guidance on when and how to consider discussing decreasing or

discontinuing antihypertensive medication when intensity of treatment may actually increase harms, and reasonably be called overtreatment. When considering community-dwelling people ≥ 70 years old with hypertension, who do not meet the inclusion criteria used for e.g. SPRINT and HYVET, these results may help inform discussion of risks and benefits and selection of most appropriate treatment targets.

Generalizability

This large study included a heterogeneous primary care population that has previously been validated as being representative of the broader Canadian population.[206] We had a follow-up period up to 11.8 years and a large number of incident dementia endpoints (n=1814). Randomized controlled trials that have been used to inform current Canadian guidelines have had more exclusive populations, and have been criticized for not being representative.[268] For example, SPRINT excluded individuals with diabetes, those who required nursing care or who had a previous stroke.[101] While our study is observational and cannot be used to define causality, our results do raise questions about the possible harms associated with treating blood pressure to <120 mmHg SBP and <70 mmHg DBP. To prevent overtreatment, adequate informed and shared decision-making should include consideration of both harms and benefits of various treatment intensities. Future rigorous study of blood pressure treatment targets in general primary care populations, with dementia and cognition as primary outcomes, are needed.

5.6 Conclusion

This study provides additional information related to the potential harms of blood pressure treatment on the risk of dementia. Specifically, our results suggest that after the age of 70, is an increase in incident dementia associated with treating SBP to <120 mmHg or DBP to <70mmHg. Studies exploring effects of maintaining treated blood pressure within specific upper and lower thresholds could delay or prevent onset of dementia.

Chapter 6: Conclusion

6.1 Treatment intensity as a new way to address polypharmacy

I began this work to learn how to provide better clinical care to patients like Mrs. B (Figure 1.1). She suffered from the effects of overtreatment of both symptomatic and asymptomatic conditions that was supported by existing published evidence. People her age with similar burdens of frailty and co-morbid diagnoses are still rarely included in research studies, yet they are prescribed the drug regimens that have only been adequately studied in younger and healthier people.[201] Traditional approaches to polypharmacy, that of drug counting and application of lists of inappropriate drugs (Figure 1.4), would likely not have made a difference given her particular set of co-morbidities.

In this dissertation, the concept of treatment intensity for asymptomatic conditions, i.e. how much treatment and to what effect, could be a valuable approach to addressing polypharmacy and overtreatment of people ≥70 years old in Canada. The studies included in this dissertation suggest that the most intense treatment of hypertension was associated with increased polypharmacy, for both nursing home patients (Chapter 3) and community-dwelling elders (Chapter 4). To explore specific harms that may be associated with varying levels of treatment intensity, I measured the associations between incident dementia and treated blood pressure (Chapter 5). This results of this study suggest treatment intensity of hypertension is a modifiable risk factor that could potentially reduce incident dementia. These compelling findings support the idea that

use of treatment intensity to guide prescribing for asymptomatic conditions could lead to a meaningful and important reduction in overtreatment.

This work has developed lines of evidence to demonstrate the potential utility of treatment intensity as a useful approach to address a) polypharmacy and b) harms of overtreatment of asymptomatic conditions in older people. Further study of treatment intensity for asymptomatic conditions could elucidate the harms and benefits of an acceptable range of treatment outcomes. Our current approach uses a binary 'treat or not treat' decision. A treatment range, with an upper and lower threshold, could encourage the consideration of targets most appropriate for each person. In the case of hypertension, the surrogate measure of systolic blood pressure (SBP) could be an indicator of when to increase or decrease the intensity of treatment (Figure 2.3). At a population level, the addition of a lower threshold as a signal of when to decrease treatment intensity, could reduce the incidence of dementia. Mrs. B may have benefited from such an approach to treatment of her asymptomatic conditions, and it is also possible that using treatment intensity could have created a cascade of decisions reconsidering her other prescribing.

6.1.1 Establishing an association between hypertension treatment intensity and polypharmacy

Study One (Chapter 3) - The nursing home-based cross-sectional study had 220 very frail, older people and used a linked dataset consisting of a full pharmacy record, paper charts and health authority acute care admission records. This exploratory study

examined general prescribing and associations with diabetes and hypertension treatment. With no consensus on measuring overtreatment, the definitions for overtreatment used in this study were created using existing literature. I found that 52% of people with diabetes were overtreated (defined as being prescribed at least one hypoglycemic medication and having an A1c of ≤7.5%) and 44% of people being treated for hypertension were overtreated (defined as SBP ≤128 mmHg and ≥1 hypertension medication). Those that had overtreated diabetes were prescribed more non-hypoglycemic medications (mean= 11.0 (SD3.7) versus 7.2 (SD3.1), p=0.01), but a similar relationship for hypertension was not statistically significant (mean= 8.4 (SD3.8) versus 7.7 (SD 2.9), p=0.285). The prevalence of diabetes and/or hypertension overtreatment (regardless of definition) had not been described in the nursing home population before, and as far as I know this study remains the only published work that looks at a potential relationship between overtreatment and more general polypharmacy.

Study Two (Chapter 4) - A similar approach was taken with 25,737 community-dwelling people ≥70 years old being treated for hypertension (hypertension) using the Canadian Primary Care Sentinel Surveillance Network (CPCSSN) dataset (Chapter 4). I found that 2300 (9%) of the sample had blood pressure treated to <120 mmHg and 48% of this group also received ≥9 non-hypertension prescriptions, versus 35% for the rest of the sample. The overtreated cohort members were also more unwell. We applied a logistic regression model, adjusted for age, sex, co-morbidities and burden of illness to observe associations with an outcome of SBP <120 versus ≥ 120 mmHg and DBP <70

versus ≥ 70 mmHg. We found that both overtreated SBP and DBP had odds ratios that were associated with increased prescribing (Figures 4.6 and 4.7) in this community-dwelling population.

6.1.2 Harm associated with increased treatment intensity of hypertension

Asymptomatic conditions are treated to reduce risk of unwanted sequelae, like strokes, heart attacks and earlier deaths. However, we lack accurate estimates of the actual risks and benefits of treatments prescribed widely in primary care, as most were tested only on more well and/or younger people.[126,201,269] Further, the inevitability of death and personal preferences about how death might occur have not been factored into traditional risk calculations for these treatments. The CPCSSN database provided an opportunity to not only describe disease frequencies and prescribing patterns, but also to observe interactions for a large pan-Canadian sample that receives primary care in the community.

Study Three (Chapter 5) - This study used an adjusted Cox proportional hazards model to estimate changes to risk of incident dementia based on how high (or low) blood pressure was treated for 24,016 people ≥70 years old. When looking at SBP as a continuous variable a 1mmHg increase in SBP was associated with a decreased risk of dementia, HR 0.991 (95%CI 0.987-0.995, p = <.0001). I found a persistent, significant increased risk of incident dementia with having SBP or DBP treated more intensely (Table 5.2-5.5). Importantly, having ≥ 3 co-morbidities also had an unexpectedly strong

association with increased dementia (for SBP as continuous, Figure 5.4, HR 8.125, (95%CI 7.011-9.416)).

6.2 Utility of research findings

6.2.1 Limitation and opportunity: accurate identification of the burden of illness

Measuring the burden of illness in primary care population and accurately describing its effect, is a new area of research. Being able to accurately identify those patients with similar observable characteristics, such as age, gender and medical co-morbidities who are more unwell versus more well does not have a consensus approach, even in prospective studies.[270] For all 3 of my studies, I relied on existing medical records created for clinical purposes. This added a layer of difficulty in creating a proxy or surrogate measure. My review of the literature suggested that it was reasonable to assume that higher values of polypharmacy,[271] blood pressure variability[213,272] and number of health record changes/blood pressure measures[225] may correlate to people who are generally more unwell. However, I found that the variable that was most reliable in these studies was a simple sum of additional co-morbidities,[224] specifically, if there were ≥3 co-morbidities, in addition to hypertension.

Calculation of ≥3 co-morbidities was straightforward using CPCSSN data. Future work to validate this as a reasonable surrogate would be a great contribution to more accurately identify those people with a higher burden of illness. Identification of a reliable measure of burden of illness will facilitate adjusting future cohort analyses for

the potential confounding influence of some cohort members simply being more unwell than their health record may otherwise indicate.

6.2.2 Harms and benefits framework for asymptomatic conditions

Being able to refine an estimate of harms and benefits for treatment of an asymptomatic condition will allow clinicians, patients, and their families to make better shared decisions. Current guideline recommendations and reviews of guidelines[273] rely heavily on expert consensus, instead of actual observations from populations receiving the treatments advised. Being able to appropriately estimate harms and benefits for people who typically are not represented in randomized clinical trials could possibly improve patient outcomes and reduce harms.

The common assumption that all prescribing to reduce risks is good, as we see with treating asymptomatic conditions like hypertension, has possibly created unexpected harm. The study by Shehab et al.[47] showed that even drug therapies not usually thought of as “potentially inappropriate” can be problematic. For example, the blood pressure medications, renin angiotensin inhibitors (ACE-I or ARB) were implicated in 2870 (or 2.9% (95%CI1.7-4.1) of all US emergency department visits for adverse drug events that resulted in hospitalization. However, there are few published estimates of harms and benefits for treatment of asymptomatic conditions in people older than 70 years. Using the model of treatment intensity, with consideration of an upper and lower threshold, the results presented in this dissertation could be considered for development of more accurate risk calculators.

6.2.3 Incorporating treatment intensity into clinical practice guidelines

High blood pressure is treated widely by primary care clinicians. These clinicians diagnose, treat, and follow patients who present with a wide array of undifferentiated illness, as well as variants of normal that may be perceived as an illness. It would be impossible for any primary care clinician to stay current on every diagnostic and treatment standard without some mechanism to synthesize the data. Clinical practice guidelines (CPGs) have emerged over the last 50 years to standardize approaches to various conditions.[274] At their best, they provide a simplified, accessible treatment pathway that saves time for clinicians and improves outcomes for many people. At their worst they may provide a treatment approach for a particular patient that is inappropriate or harmful.[143] The work described in this dissertation provides a) an estimate of specific harms for people ≥70 years old being treated for hypertension and b) more generally, an approach to studying effects of disease treatment in primary care, on a heterogeneous population that is unlikely to ever be represented in clinical trials.

Figure 4.4 shows that 24% (53,231/217,540) of Canadians ≥70 years old are being treated for hypertension in primary care. At least 27% of this group would have been excluded from SPRINT due to a concurrent diagnosis of diabetes. Frailty, dementia, kidney disease and CHF are also common reasons to be excluded from hypertension trials (Table 2.3). By developing this CPCSSN cohort, representative of “typical”

Canadian primary care patients,[205] we are able to observe prevalence of harms and benefits in a fashion that could increase the accuracy of individual estimates.

Similarly, Chapter 4 informs us that 66% of the cohort has an achieved blood pressure <140 mmHg and would be considered "controlled" as defined by some previous studies.[110] Having access to information about treatment agents and outcomes (treatment intensity) also allows for a more robust and accurate population description of hypertension treatment in Canada.

6.2.3.1 De-intensification of treatment

Clinical Practice Guidelines (CPGs) typically have only limited guidance for de-intensifying treatment. They usually emphasize intensification, often with only a single disease perspective (i.e. not acknowledging the presence or possible effects of multimorbidity). Markovitz et al. reviewed 22 American guidelines for diabetes and cardiovascular diseases (including hypertension) and found that of the total 361 recommendations that were made, only 105 (29%) could be classified as de-intensification.[275] They found substantial variability in how de-intensification was presented in guidelines and that even when evidence was considered weak, recommendations for intensification were more numerous. Instead, they suggest that the imbalance could be explained by "the widespread predilection for generalizing benefits in homogenous populations to broader populations."[276] As described in section 2.5.1 of this dissertation, there are some examples of how inappropriate this approach can be. The fallout from the application of a RALES study finding for use of

spironolactone in advanced heart failure[132] to a heterogeneous community-based population resulted in increased hospitalizations and deaths.[133]

We have only a handful of studies, mostly on diabetes patients, that have reported on frequency of blood pressure treatment intensity and subsequent de-intensification.[97] There is also little research about the effects of de-prescribing of blood pressure medications to guide this work. van der Wardt et al.[277] conducted a review of 66 heterogeneous studies of discontinuation of hypertension medications and found that at 2 years, in 26% (95%CI 26-27%) remained "successfully withdrawn from [blood pressure] medications". However, the diversity of these studies makes summary data difficult to interpret.

6.2.3.2 Current Canadian guidelines

The SPRINT trial has introduced a blood pressure treatment target of <120 mmHg more widely.[278] In Canada, the CHEP guidelines have been modified to include consideration of the lower target,[96] but does not mention a threshold at which de-intensification should be considered. The 2017 guideline has also removed the suggestion that there should be different goals for the elderly, because "evidence suggests that older patients with hypertension benefit similarly from intensive BP reductions as younger adults". This recommendation only cites findings from randomized control trials.[100,279–281] There is no guidance about when or how to de-intensify treatment, nor what the harms and benefits of doing so might be.

6.2.3.3 Addition of a lower treatment threshold to treatment guidelines

The findings of increased polypharmacy associated with blood pressure being treated to lower SBP and DBP, as well as increased incidence of dementia, are important potential harms that could change a clinical recommendation or the course of a shared decision about treatment goals. Addition of a lower threshold, at which harms likely exceed benefits, could provide a range of most appropriate treatment. To my knowledge, only one hypertension guideline has included a lower threshold.[149]

In light of the possible increased harm of incident dementia with increased treatment intensity, the potential to modify this risk factor is intriguing. A lower threshold of 120 mmHg could affect as many as 9% of those ≥70 years old currently treated for hypertension in Canada. The potential risk reduction for the composite outcome (myocardial infarction, acute coronary syndrome, acute decompensated heart failure or death from CV causes) measured in SPRINT, 5.2%, vs. 6.8% in the standard BP target group, RR 0.76 [0.65, 0.90], ARR 1.6%, NNT 63 for 3.3 years. Given the poor prognosis and limited treatment options for dementia, an opportunity to reduce the risk of dementia by choosing a higher treatment target (lower treatment intensity) could be well received by appropriate patients and providers.

6.3 Limitations

The results of these studies should be interpreted with caution. The relationship between polypharmacy and overtreatment of asymptomatic conditions is nascent. And while the study of the relationship between blood pressure treatment and incident

dementia is more developed, there is no consensus on the exact nature and direction of the connection. Observational studies cannot reliably identify causality.

The datasets used for these studies were constructed from information collected for other purposes (primary care encounters). The ability to create ideal variables was limited by the use of secondary data. For example, the diagnosis of dementia relied on an algorithm with high sensitivity and specificity.[290] But, there was no mechanism to identify early stages of cognitive change. Mossello et al.[191] found an increased cognitive decline with increased blood pressure treatment intensity in those who already have cognitive impairment. We were unable to measure progress of cognitive change and it is possible that clinically meaningful cognitive change was underestimated as we could not detect it early enough.[282]

Prescribing information in the CPCSSN database was limited only to prescription details, not whether the drugs were dispensed, nor if consumed. There is current work to link CPCSSN records to dispensing data in British Columbia. Future studies that can validate assumptions about prescriptions being dispensed will be valuable to better understanding actual exposures. Similarly, this work had limited resources for data programming and we were unable to create a robust process to count all repeated prescriptions. Instead a total number of prescriptions over a two-year period was used as a surrogate. It would be a valuable addition to CPCSSN to have a programmed algorithm for more accurate drug counting. The elements identified in Figure 1.3 could be used to establish the algorithm.

6.3.1 Missing data

Data collected for clinical purposes is known to have higher prevalence of missing data.[283] For this work, having only partially reported data on smoking status, and inability to report neither on length of time of having a diagnosis of hypertension nor socio-economic status may have had confounding effects that could alter the results.

6.3.1.1 Smoking

Smoking is a well-known risk factor for many negative health outcomes, including hypertension[284] and dementia.[285] Identification of smoking history and provision of treatment for smoking cessation is a common clinical activity in primary care, however, there are not documentation standards nor diagnosis codes in common use to facilitate identification of this important piece of medical history.[286] In this work, we found that only 32% of cohort members had a smoking history identified in their record. This is consistent with other assessments of primary health care records.[287] Given the health effects of tobacco and the benefits seen with tobacco cessation, it is unlikely that primary care clinicians are not including this element in their treatment plans. Rather, the CPCSSN dataset does not have an accurate way to identify the activity. For this work, it also means that we could not test whether smoking status had an impact on time to dementia in the cox model presented in Chapter 5.

6.3.1.2 Timing of individuals' diagnosis of hypertension

Being diagnosed with hypertension in mid-life versus in later life has been postulated to have a different effect on incident dementia.[172] There are few longitudinal studies that have followed hypertension treatment from middle age to older age. In the studies that are available there appears to be an increased incidence of dementia (OR 2.8 (95%CI 1.1-7.2)) in older age if SBP in >160 mmHg (versus <140 mmHg).[288] While there is not a clear answer about this, being able to include it as a variable in the cox proportional hazards analysis for Chapter 5 would have been a very valuable contribution to the literature.

The CPCSSN database currently does not have a reliable way to identify the first date of most diagnoses. The date of diagnosis of dementia is a special case given there are a set of drugs uniquely used for treatment of dementia and that the disease only rarely occurs before the age of 70. Parkinson's disease has a similar profile and likewise can be identified with high specificity and sensitivity. Exact, or even approximate, date of diagnosis of hypertension has some specific challenges. "Mid-life" hypertension usually refers to age ~40-65 and CPCSSN records only go back to the time when a provider started using their electronic health record (EHR), e.g. If a provider got their EHR in 2002, only records generated from that time forward to the date of data extraction (June 30, 2015) would be included, meaning the date of incident hypertension may already be several years past.

Future work may benefit from exploring this, and perhaps examining the historical blood pressure readings to be able to describe the course of blood pressure over the available record. This dissertation looked specifically at the role of treated hypertension, and it may be possible to combine historical blood pressure readings with first incidence of prescription of any one class of antihypertensives as a possible indicator of incident hypertension.

6.3.1.3 Socio-economic status

In contrast to smoking, socio-economic status is not routinely reported in primary care records. This is despite the well-described effects on almost all health outcomes,[289] including dementia.[290] At present, there are no indicators to reliably report socioeconomic status on clinical records in CPCSSN. A designed study with primary data collection could address such an absence and the information could be factored into a model like the one presented in Chapter 5.

6.3.2 Potential future methods to mitigate effect of missing data

The above specific limitations regarding data quality and availability could be addressed with the use of a randomization process, which would decrease or eliminate possible bias that could be arising from the inability to identify these elements as confounders. Other study designs, such as creating a comparator group, where people without a specific diagnosis of hypertension, (but with blood pressures still recorded in CPCSSN data), could be compared to those with treated blood pressure for associations with polypharmacy and incident dementia, could help mitigate some of the possible

confounding described above. This work ended up looking almost exclusively on treated blood pressure, which while it created a cohort of comparable individuals, it may also have introduced a sampling bias that comparison to a “non-treatment” group could help reveal.

6.3.3 Sample size in nursing home study

The sample size in the nursing home study was small, which limited the type of analysis that we could effectively do. We only sampled a particular kind of facility (publicly run, hospital-affiliated), which has been found to offer the highest standard of care[291] but is likely not representative of care provided at all nursing homes in British Columbia or the rest of Canada.

6.3.4 Lack of data linkage

The CPCSSN dataset was not linked to important additional data sources, including: pharmacy dispensing, acute care use, vital statistics (for deaths), nursing home admissions, home care use, etc. As a result, we have only a limited picture of the cohort members. For the cox model in Chapter 5, censoring variables were unable to incorporate death or hospitalization both of which are a) common in this age group and b) directly linked to a diagnosis of dementia. Future work in this area would ideally be able to incorporate linked data. Such linkages are in process for data collected in British Columbia, Ontario and Manitoba.

6.4 Next steps

Developing appropriate definitions of treatment intensity, combined with the use of both lower and upper thresholds to guide specific treatment decisions for asymptomatic conditions, could reduce overtreatment in people ≥70 years old. Additional study of hypertension, as well as other common asymptomatic conditions, such as diabetes and osteoporosis, should include: defining parameters of treatment intensity (e.g. surrogates and medicines prescribed), accurately describing various levels of treatment intensity, and the harms and benefits observed at each level/increment. These studies should include a representative sample of the population that is as inclusive as possible. Ideally, the sample would be large enough to allow for exploration of subgroup effects.

This work found a persistent association between the most intensely treated blood pressure and higher general prescribing, however the harms of such an association with polypharmacy are not easy to specify. In contrast, if the increased harm of an earlier diagnosis of dementia due to a lower achieved blood pressure, is be found to be true, this could have wide spread effects on how hypertension is treated in Canadians older than 70.Though the associations found in this dissertation were small, it directly challenge how the benefits of a lower target, like the one used in SPRINT, are being portrayed and integrated into the American[292] and Canadian.[96] Repeating this study in other data sets to see if the result is replicable would be very valuable.

In conclusion, polypharmacy, overtreatment and treatment intensity are overlapping concepts that have been developed in this dissertation, but still lack precise, robust

definitions. Progressing these definitions, towards consensus, and using them in well-designed studies, with patient-centered outcomes applicable to heterogenous populations, requires ongoing focus and debate. This dissertation has provided a framework of the scope and considerations that are required and that this framework could be used by other researchers to design studies that will benefit people ≥70 years old, like Mrs. B, facing possible harms from treatment intensity of asymptomatic conditions.

Appendix A - Changes to research plan for doctoral studies

Proposed randomized controlled trial of deprescribing

In June 2011, I enrolled in the UBC Department of Family Medicine Clinician Scholar program where Dr. Scott Garrison agreed to provide mentorship. We discussed the idea of a randomized controlled trial to assess patient-oriented outcomes, like morbidity and mortality, with a systematic process of deprescribing. I stepped away from this project in July 2011 for a maternity leave and when I returned in September 2012, Dr. Garrison encouraged me to do this work as part of the requirements for a PhD offered at UBC by Experimental Medicine. This would provide structure and access to the classes I needed to gain skills in quantitative analysis. Dr. Margaret McGregor, a fellow GP and researcher with experience studying nursing home populations, and Dr. James McCormack, a professor in Pharmaceutical Sciences and expert in translation of research to clinical practice, also agreed to be on my committee.

Over the next year, while continuing my practice part-time and taking the PhD courses, I wrote up the research protocols and obtained required permissions from the UBC Clinical Research Ethics Board and the facilities where we would be recruiting patients. We would use six well-regarded, hospital-affiliated nursing homes in Richmond and Vancouver. With all materials complete and permissions gathered, we began recruiting patients in the summer of 2013.

Unfortunately, after approaching 40 families, we failed to recruit a single person. Almost all residents in BC nursing homes are affected by dementia and, as such, we needed to use proxy decision-makers to consent. The proxy refusals fell into two general categories: “My loved one has an excellent doctor, I am sure that s/he needs every medication prescribed” and “s/he has been through enough, I don’t want my loved one to be a guinea pig”. In hindsight, these responses were reasonable given the lack of public discourse about polypharmacy and deprescribing and the emotionally intense idea of a vulnerable loved one possibly being given medicines that could harm them. We stopped the trial and reflected on the intentions of the project. In early 2014, I took an RCT design course and a research ethics course to consider if there was a way to restructure the project to have it be successful. As shown in the below Figure, despite efforts to redesign the trial, we ultimately decided that given the poor general public knowledge of polypharmacy, the ethical requirement to use proxy decision makers, my academic timeline and resources available, it would not be possible to run a successful trial at this time.

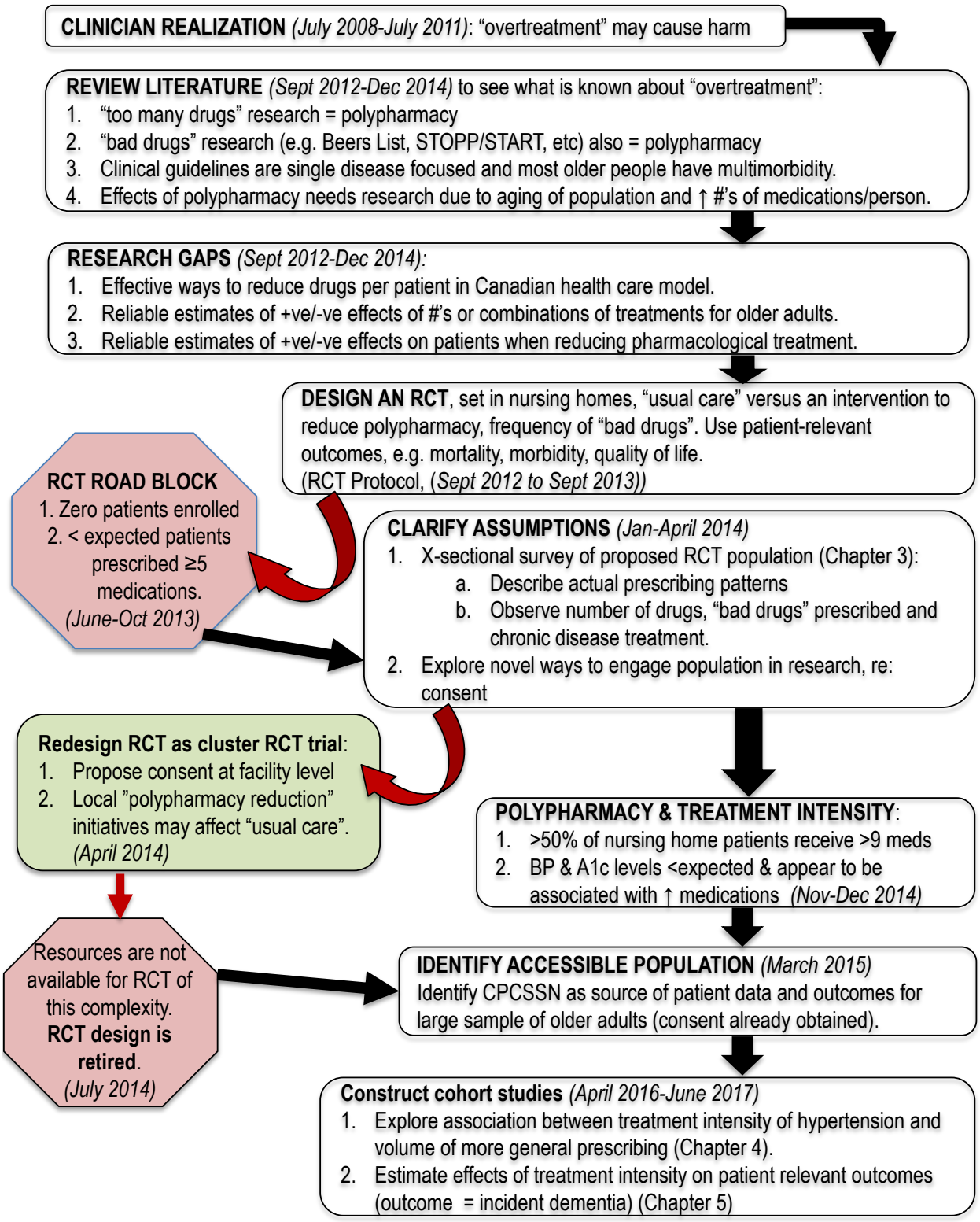


Figure: Evolution of my program of research

Appendix B - Data sources and collection plan for cross sectional study

Objectives for Data collection:
Provide baseline information about existing prescribing practices in 6 designated residential care facilities, specifically, the prevalence of polypharmacy.
Detect signals about risks and benefits of numbers and classes of medications.
Help inform elements needed for an economic model of the impact of polypharmacy and potential savings of reductions that may be clinically relevant.
Provide community level data for design of a more informative pragmatic clinical trial.
Potentially provide information to immediately change clinical practice and administrative policies.

Summary List of all data collected per patient
(details of sources and methods below):

1	Name	for matching records between data sources, removed in dataset used for analysis
2	Health Insurance number and hospital unique identifier	for matching records between data sources, removed in dataset used for analysis
3	Sex	Female or male
4	Date of birth	To calculate AGE to nearest year, removed in dataset used for analysis
5	Facility	Transformed into numbered categorical variable, for comparison of patterns between facilities.
6	Precise location in facility	Needed to locate paper chart, removed in dataset used for analysis
7	Prescribing/Attending physician	Transformed into numbered categorical variable, for comparison of patterns between prescribers.
8	All medications prescribed	drug name, drug dose, drug dose frequency, whether given regular or per re nata (PR).
9	# of patient transfers to acute care in previous 12 month period	Also included, dates of each transfer – to determine acute care episodes happened before or after admission to nursing home.
10	Code status	Transformed into a transfer/no transfer variable. Health authorities use a shared “do not attempt resuscitation” template, previous research has identified level 1 and 2 to mean “no transfers to acute care”, and 3 and higher to be “transfer to acute care”.
11	Last recorded HgbA1c	Percent, %
12	Last recorded blood pressure	Systolic/diastolic, mmHg
13	Presence of a diagnosis of dementia, hypertension, diabetes or congestive heart failure	– yes or no – listed as diagnosis in paper chart
14	Date of first admission to facility	Transformed into a “length of stay” variable.

POPULATION – random sample of frail elders living in all 5 Providence Healthcare (PHC) residential care facilities and the Minoru residential care (Vancouver Coastal Health (VCH) –Richmond)

RESEARCH DESIGN - Cross sectional survey retrospective patient data available on existing hospital and pharmacy databases and patient charts. Measured at a single time point in time for prevalence of polypharmacy. The single point in time must be identified as close as possible to first day of data collection beginning given the significant fluctuation to how pharmacy data is presented in the regional health authority databases (i.e. records are overwritten, rather than saved as a day by day snapshot). Once ethics and institutional approval are obtained, a specific date in the near future will be chosen (i.e. within 4 weeks of approval.) The 12 month period requested from Decision Support for the mortality and transfers data will be measured backwards from the specified date.

DATA SOURCE #1 - Decision Support (regional BC health authority patient database, "EDAD")
For 1 year period prior to date on which prescription data is collected:

- # of transfers to acute care and/or admissions to hospital

DATA SOURCE #2 - Regional health authority (PHC and VCH) pharmacy databases
List of pharmacy data a specified single date close to the time of request (i.e. once ethics approved and VCRI approval obtained) includes:

- Date of birth
- Health insurance number (to be used exclusively for data matching with Decision Support and paper charts)
- Attending MD
- Exact facility location (used to group data by facility and to direct researcher to appropriate location to collect chart data)
- Sex
- Medications
    - Name of each drug prescribed
    - Whether it is regular or PRN
    - Dose
    - Dosing frequency

DATA SOURCE #3 - Patient paper chart: (to be collected by PI or med student research assistant). Patient name, (first and last) and specific facility location will be needed to select the correct paper chart as that is how they are organized at facility. A sample data collection sheet is included below and includes:

1. Date of admission to facility (unavailable from computer systems due to "restart" of clinical record every time a patient is transferred to acute care for both Decision Support and pharmacy databases)

2. DNAR status noted on Level of Intervention form (assumed to be a very strong predictor of # of transfers, also suspected to be associated with less pharmaceutically intense care of patients)
3. Most recent HgbA1c from last 6 months (to check associations with # and dosing of hypoglycemic drugs)
4. Most recent BP from last 6 months (to check associations with # and dosing of antihypertensive drugs)
5. Diagnoses
    a. any variant of dementia
    b. hypertension
    c. diabetes
    d. congestive heart failure

References

1. Bean RB. Sir William Osler : Aphorisms from His Bedside Teachings and Writings.

2. Rhodes P. Medical nemesis--three views. Indictment of medical care. British Medical Journal. 1974 Dec 7;4(5944):576.

3. Salzman C. Psychotropic drug use and polypharmacy in a general hospital. General Hospital Psychiatry. 1981 Mar;3(1):1–9.

4. Larson EB, Kukull WA, Buchner D, Reifler BV. Adverse drug reactions associated with global cognitive impairment in elderly persons. Annals Of Internal Medicine. 1987 Aug;107(2):169–73.

5. Gurwitz JH, Avorn J. The ambiguous relation between aging and adverse drug reactions. Ann Intern Med. 1991 Jun 1;114(11):956–66.

6. Vogel L. Two-thirds of seniors in long-term care take 10 or more drugs: CIHI. CMAJ. 2014 Jun 10;186(9):E309–E309.

7. McCracken R, McCormack J, McGregor MJ, Wong ST, Garrison S. Associations between polypharmacy and treatment intensity for hypertension and diabetes: a cross-sectional study of nursing home patients in British Columbia, Canada. BMJ Open. 2017 Aug 11;7(8):e017430.

8. Birtwhistle R, Keshavjee K, Lambert-Lanning A, Godwin M, Greiver M, Manca D, et al. Building a Pan-Canadian Primary Care Sentinel Surveillance Network: Initial Development and Moving Forward. J Am Board Fam Med. 2009 Jul 1;22(4):412–22.

9. Page AT, Clifford RM, Potter K, Schwartz D, Etherton-Beer CD. The feasibility and effect of deprescribing in older adults on mortality and health: a systematic review and meta-analysis. Br J Clin Pharmacol. 2016 Sep;82(3):583–623.

10. Veronese N, Stubbs B, Noale M, Solmi M, Pilotto A, Vaona A, et al. Polypharmacy Is Associated With Higher Frailty Risk in Older People: An 8-Year Longitudinal Cohort Study. J Am Med Dir Assoc. 2017 Apr 7;

11. Konrat C, Boutron I, Trinquart L, Auleley G-R, Ricordeau P, Ravaud P. Underrepresentation of Elderly People in Randomised Controlled Trials. The Example of Trials of 4 Widely Prescribed Drugs. PLOS ONE. 2012 Mar 30;7(3):e33559.

12. McMurdo MET, Witham MD, Gillespie ND. Including older people in clinical research: Benefits shown in trials in younger people may not apply to older people. BMJ : British Medical Journal. 2005 Nov 5;331(7524):1036.

13. Sera LC, McPherson ML. Pharmacokinetics and Pharmacodynamic Changes Associated with Aging and Implications for Drug Therapy. Clinics in Geriatric Medicine. 2012 May;28(2):273–86.

14. Reeve E, Trenaman SC, Rockwood K, Hilmer SN. Pharmacokinetic and pharmacodynamic alterations in older people with dementia. Expert Opin Drug Metab Toxicol. 2017 Jun;13(6):651–68.

15. Musso CG, Belloso WH, Scibona P, Bellizzi V, Macias Nunez JF. Impact of renal aging on drug therapy. Postgrad Med. 2015 Aug;127(6):623–9.

16. Mallet L, Spinewine A, Huang A. The challenge of managing drug interactions in elderly people. The Lancet. 2007 Jul 20;370(9582):185–91.

17. Merle L, Laroche M-L, Dantoine T, Charmes J-P. Predicting and preventing adverse drug reactions in the very old. Drugs Aging. 2005;22(5):375–92.

18. Goedken AM, Lund BC, Cook EA, Schroeder MC, Brooks JM. Application of a framework for determining number of drugs. BMC Res Notes. 2016;9(1):272.

19. Guthrie B, McCowan C, Davey P, Simpson CR, Dreischulte T, Barnett K. High risk prescribing in primary care patients particularly vulnerable to adverse drug events: cross sectional population database analysis in Scottish general practice. BMJ. 2011 Jun 21;342:d3514.

20. Fincke BG, Snyder K, Cantillon C, Gaehde S, Standring P, Fiore L, et al. Three complementary definitions of polypharmacy: methods, application and comparison of findings in a large prescription database. Pharmacoepidem Drug Safe. 2005 Feb 1;14(2):121–8.

21. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. BMC Geriatr [Internet]. 2017 Oct 10 [cited 2018 Jan 25];17. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5635569/

22. Mortazavi SS, Shati M, Keshtkar A, Malakouti SK, Bazargan M, Assari S. Defining polypharmacy in the elderly: a systematic review protocol. BMJ Open. 2016 Mar 1;6(3):e010989.

23. Chang C-B, Chan D-C. Comparison of published explicit criteria for potentially inappropriate medications in older adults. Drugs Aging. 2010 Dec 1;27(12):947–57.

24. Corsonello A, Onder G, Abbatecola AM, Guffanti EE, Gareri P, Lattanzio F. Explicit criteria for potentially inappropriate medications to reduce the risk of adverse drug reactions in elderly people: from Beers to STOPP/START criteria. Drug Saf. 2012 Jan;35 Suppl 1:21–8.

25. Beers MH, Ouslander JG, Rollingher I, Reuben DB, Brooks J, Beck JC. Explicit criteria for determining inappropriate medication use in nursing home residents. UCLA Division of Geriatric Medicine. Arch Intern Med. 1991 Sep;151(9):1825–32.

26. American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc. 2015 Nov 1;63(11):2227–46.

27. Holmes HM, Sachs GA, Shega JW, Hougham GW, Cox Hayley D, Dale W. Integrating Palliative Medicine into the Care of Persons with Advanced Dementia: Identifying Appropriate Medication Use. Journal of the American Geriatrics Society. 2008 Jul 1;56(7):1306–11.

28. Tjia J, Briesacher BA, Peterson D, Liu Q, Andrade SE, Mitchell SL. Use of medications of questionable benefit in advanced dementia. JAMA Intern Med. 2014 Nov 1;174(11):1763–71.

29. Parsons C. Polypharmacy and inappropriate medication use in patients with dementia: an underresearched problem. Ther Adv Drug Saf. 2017 Jan;8(1):31–46.

30. Todd A, Husband A, Andrew I, Pearson S-A, Lindsey L, Holmes H. Inappropriate prescribing of preventative medication in patients with life-limiting illness: a systematic review. BMJ Support Palliat Care. 2016 Jan 5;

31. Morin L, Laroche M-L, Texier G, Johnell K. Prevalence of Potentially Inappropriate Medication Use in Older Adults Living in Nursing Homes: A Systematic Review. Journal of the American Medical Directors Association [Internet]. 2016 Jul 27 [cited 2016 Aug 1];0(0). Available from: /article/S1525-8610(16)30218-3/abstract

32. Cooper JA, Cadogan CA, Patterson SM, Kerse N, Bradley MC, Ryan C, et al. Interventions to improve the appropriate use of polypharmacy in older people: a Cochrane systematic review. BMJ Open [Internet]. 2015 Dec 9 [cited 2016 Jan 23];5(12). Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4679890/

33. Moriarty F, Hardy C, Bennett K, Smith SM, Fahey T. Trends and interaction of polypharmacy and potentially inappropriate prescribing in primary care over 15 years in Ireland: a repeated cross-sectional study. BMJ Open [Internet]. 2015 Sep 16 [cited 2017 Apr 28];5(9). Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4577876/

34. Jirón M, Pate V, Hanson LC, Lund JL, Jonsson Funk M, Stürmer T. Trends in Prevalence and Determinants of Potentially Inappropriate Prescribing in the United States: 2007 to 2012. J Am Geriatr Soc. 2016 Apr;64(4):788–97.

35. Qato DM, Wilder J, Schumm LP, Gillet V, Alexander GC. Changes in Prescription and Over-the-Counter Medication and Dietary Supplement Use Among Older Adults in the United States, 2005 vs 2011. JAMA internal medicine. 2016 Apr;176(4):473.

36. Payne RA, Abel GA, Avery AJ, Mercer SW, Roland MO. Is polypharmacy always hazardous? A retrospective cohort analysis using linked electronic health records from primary and secondary care. Br J Clin Pharmacol. 2014 Jun;77(6):1073–82.

37. Alabousi M, Abdullah P, Alter DA, Booth GL, Hogg W, Ko DT, et al. Cardiovascular Risk Factor Management Performance in Canada and the United States: A Systematic Review. Can J Cardiol. 2017 Mar;33(3):393–404.

38. Cherubini A, Corsonello A, Lattanzio F. Underprescription of beneficial medicines in older people: causes, consequences and prevention. Drugs Aging. 2012 Jun 1;29(6):463–75.

39. Cherubini A, Corsonello A, Lattanzio F. Polypharmacy in Nursing Home Residents: What Is the Way Forward? J Am Med Dir Assoc. 2016 Jan;17(1):4–6.

40. Steinman MA. Polypharmacy—time to get beyond numbers. JAMA Intern Med [Internet]. 2016 Mar 21 [cited 2016 Mar 21]; Available from: http://dx.doi.org/10.1001/jamainternmed.2015.8597

41. Tamura BK, Bell CL, Inaba M, Masaki KH. Outcomes of polypharmacy in nursing home residents. Clin Geriatr Med. 2012 May;28(2):217–36.

42. Fried TR, O'Leary J, Towle V, Goldstein MK, Trentalange M, Martin DK. Health outcomes associated with polypharmacy in community-dwelling older adults: a systematic review. J Am Geriatr Soc. 2014 Dec;62(12):2261–72.

43. Gallacher KI, Batty GD, McLean G, Mercer SW, Guthrie B, May CR, et al. Stroke, multimorbidity and polypharmacy in a nationally representative sample of 1,424,378 patients in Scotland: implications for treatment burden. BMC Med [Internet]. 2014 Oct 3 [cited 2015 Aug 26];12. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4220053/

44. Kozak JF, Mithani, Akber. Prevalence of Adverse Drug Events in Long Term Care: Variations in Screening Between Nurses and Physician-Pharmacist Reviewers. J Gerontol Geriatr Med. 2015;1(007).

45. Gurwitz JH, Field TS, Harrold LR, et al. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. JAMA. 2003 Mar 5;289(9):1107–16.

46. Shehab N, Lovegrove MC, Geller AI, Rose KO, Weidle NJ, Budnitz DS. US Emergency Department Visits for Outpatient Adverse Drug Events, 2013-2014. JAMA. 2016 Nov 22;316(20):2115–25.

47. Corlan D. Tells you how many medline entries for a certain term in a certain year [Internet]. MedLineTrend. Available from: http://dan.corlan.net/medline-trend.html

48. Gallagher P, Ryan C, Byrne S, Kennedy J, O'Mahony D. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. Int J Clin Pharmacol Ther. 2008 Feb;46(2):72–83.

49. Iyer S, Naganathan V, McLachlan AJ, Le Couteur DG. Medication withdrawal trials in people aged 65 years and older: a systematic review. Drugs Aging. 2008;25(12):1021–31.

50. Patterson SM, Cadogan CA, Kerse N, Cardwell CR, Bradley MC, Ryan C, et al. Interventions to improve the appropriate use of polypharmacy for older people. Cochrane Database Syst Rev. 2014;10:CD008165.

51. Alldred DP, Raynor DK, Hughes C, Barber N, Chen TF, Spoor P. Interventions to optimise prescribing for older people in care homes. Cochrane Database Syst Rev. 2013 Feb 28;(2):CD009095.

52. Forsetlund L, Eike MC, Gjerberg E, Vist GE. Effect of interventions to reduce potentially inappropriate use of drugs in nursing homes: a systematic review of randomised controlled trials. BMC Geriatr. 2011 Apr 17;11:16.

53. Tjia J, Velten SJ, Parsons C, Valluri S, Briesacher BA. Studies to reduce unnecessary medication use in frail older adults: a systematic review. Drugs Aging. 2013 May;30(5):285–307.

54. Parsons C, Hughes CM, Passmore AP, Lapane KL. Withholding, discontinuing and withdrawing medications in dementia patients at the end of life: a neglected problem in the disadvantaged dying? Drugs Aging. 2010 Jun 1;27(6):435–49.

55. Potter K, Flicker L, Page A, Etherton-Beer C. Deprescribing in Frail Older People: A Randomised Controlled Trial. PLoS ONE. 2016;11(3):e0149984.

56. Garfinkel D, Zur-Gil S, Ben-Israel J. The war against polypharmacy: a new cost-effective geriatric-palliative approach for improving drug therapy in disabled elderly people. Isr Med Assoc J. 2007 Jun;9(6):430–4.

57. Abad-Díez JM, Calderón-Larrañaga A, Poncel-Falcó A, Poblador-Plou B, Calderón-Meza JM, Sicras-Mainar A, et al. Age and gender differences in the prevalence and patterns of multimorbidity in the older population. BMC Geriatr. 2014;14:75.

58. Boyd CM, Darer J, Boult C, Fried LP, Boult L, Wu AW. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: Implications for pay for performance. JAMA. 2005 Aug 10;294(6):716–24.

59. Guthrie B, Payne K, Alderson P, McMurdo MET, Mercer SW. Adapting clinical guidelines to take account of multimorbidity. The BMJ. 2012 Oct 4;345:e6341.

60. Mangin D, Heath I, Jamoulle M. Beyond diagnosis: rising to the multimorbidity challenge. BMJ. 2012 Jun 13;344:e3526.

61. Lee PY, Alexander KP, Hammill BG, Pasquali SK, Peterson ED. Representation of elderly persons and women in published randomized trials of acute coronary syndromes. JAMA. 2001 Aug 8;286(6):708–13.

62. Kanagaratnam L, Dramé M, Trenque T, Oubaya N, Nazeyrollas P, Novella J-L, et al. Adverse drug reactions in elderly patients with cognitive disorders: A systematic review. Maturitas. 2016 Mar;85:56–63.

63. Brahma DK, Wahlang JB, Marak MD, Ch Sangma M. Adverse drug reactions in the elderly. J Pharmacol Pharmacother. 2013 Apr;4(2):91–4.

64. Walker J, Wynne H. Review: the frequency and severity of adverse drug reactions in elderly people. Age Ageing. 1994 May;23(3):255–9.

65. Wastesson JW, Oksuzyan A, von Bornemann Hjelmborg J, Christensen K. Changes in Drug Use and Polypharmacy After the Age of 90: A Longitudinal Study of the Danish 1905 Cohort. J Am Geriatr Soc. 2017 Jan;65(1):160–4.

66. World Health Organization. WHO | World report on ageing and health [Internet]. World Health Organization; 2015 [cited 2017 May 2]. Report No.: ISBN: 9789241565042. Available from: http://www.who.int/ageing/publications/world-report-2015/en/

67. Mcgrail K, Green B, Barer ML, Evans RG, Hertzman C, Normand C. Age, costs of acute and long-term care and proximity to death: evidence for 1987-88 and 1994-95 in British Columbia. Age Ageing. 2000 May;29(3):249–53.

68. Bloom DE, Chatterji S, Kowal P, Lloyd-Sherlock P, McKee M, Rechel B, et al. Macroeconomic implications of population ageing and selected policy responses. Lancet. 2015 Feb 14;385(9968):649–57.

69. Cahir C, Fahey T, Teeling M, Teljeur C, Feely J, Bennett K. Potentially inappropriate prescribing and cost outcomes for older people: a national population study. Br J Clin Pharmacol. 2010 May;69(5):543–52.

70. Hovstadius B, Petersson G. The impact of increasing polypharmacy on prescribed drug expenditure-a register-based study in Sweden 2005-2009. Health Policy. 2013 Feb;109(2):166–74.

71. Buta BJ, Walston JD, Godino JG, Park M, Kalyani RR, Xue Q-L, et al. Frailty assessment instruments: Systematic characterization of the uses and contexts of highly-cited instruments. Ageing Res Rev. 2016 Mar;26:53–61.

72. Rockwood K. A global clinical measure of fitness and frailty in elderly people. Canadian Medical Association Journal. 2005 Aug 30;173(5):489–95.

73. Buckinx F, Rolland Y, Reginster J-Y, Ricour C, Petermans J, Bruyère O. Burden of frailty in the elderly population: perspectives for a public health challenge. Arch Public Health [Internet]. 2015 Apr 10 [cited 2016 Mar 5];73(1). Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4392630/

74. Vermeiren S, Vella-Azzopardi R, Beckwée D, Habbig A-K, Scafoglieri A, Jansen B, et al. Frailty and the Prediction of Negative Health Outcomes: A Meta-Analysis. J Am Med Dir Assoc. 2016 Dec 1;17(12):1163.e1-1163.e17.

75. Herr M, Robine J-M, Pinot J, Arvieu J-J, Ankri J. Polypharmacy and frailty: prevalence, relationship, and impact on mortality in a French sample of 2350 old people. Pharmacoepidemiol Drug Saf. 2015 Jun;24(6):637–46.

76. Pialoux T, Goyard J, Lesourd B. Screening tools for frailty in primary health care: a systematic review. Geriatr Gerontol Int. 2012 Apr;12(2):189–97.

77. Woo J, Leung J, Morley JE. Comparison of frailty indicators based on clinical phenotype and the multiple deficit approach in predicting mortality and physical limitation. J Am Geriatr Soc. 2012 Aug;60(8):1478–86.

78. Mitnitski A, Fallah N, Rockwood MRH, Rockwood K. Transitions in cognitive status in relation to frailty in older adults: a comparison of three frailty measures. J Nutr Health Aging. 2011 Dec;15(10):863–7.

79. Erkinjuntti T, Ostbye T, Steenhuis R, Hachinski V. The effect of different diagnostic criteria on the prevalence of dementia. N Engl J Med. 1997 Dec 4;337(23):1667–74.

80. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: A systematic review and metaanalysis. Alzheimer's & Dementia. 2013 Jan;9(1):63-75.e2.

81. Alzheimer Society of Canada. Rising Tide: The Impact of Dementia on Canadian Society [Internet]. Toronto, ON; 2010 [cited 2015 Aug 26]. Available from: www.alzheimer.ca/~/media/Files/national/Advocacy/ASC_Rising_Tide_Full_Report_e.pdf

82. Birks J. Cholinesterase inhibitors for Alzheimer's disease. In: The Cochrane Collaboration, editor. Cochrane Database of Systematic Reviews [Internet]. Chichester, UK: John Wiley & Sons, Ltd; 2006 [cited 2015 Jul 23]. Available from: http://doi.wiley.com/10.1002/14651858.CD005593

83. Bunn F, Burn A-M, Goodman C, Rait G, Norton S, Robinson L, et al. Comorbidity and dementia: a scoping review of the literature. BMC Medicine. 2014;12:192.

84. Park H-Y, Park J-W, Song HJ, Sohn HS, Kwon J-W. The Association between Polypharmacy and Dementia: A Nested Case-Control Study Based on a 12-Year Longitudinal Cohort Database in South Korea. PLoS ONE. 2017;12(1):e0169463.

85. Mangin D, Sweeney K, Heath I. Preventive health care in elderly people needs rethinking. BMJ. 2007 Aug 11;335(7614):285–7.

86. Heath I. Role of fear in overdiagnosis and overtreatment—an essay by Iona Heath. The BMJ. 2014 Oct 24;349:g6123.

87. Gray SL, Anderson ML, Dublin S, Hanlon JT, Hubbard R, Walker R, et al. Cumulative Use of Strong Anticholinergics and Incident Dementia: A Prospective Cohort Study. JAMA Intern Med. 2015 Mar 1;175(3):401–7.

88. Launer LJ, Hughes T, Yu B, Masaki K, Petrovitch H, Ross GW, et al. Lowering midlife levels of systolic blood pressure as a public health strategy to reduce late-life dementia: perspective from the Honolulu Heart Program/Honolulu Asia Aging Study. Hypertension. 2010 Jun;55(6):1352–9.

89. Peters R, Beckett N, Forette F, Tuomilehto J, Clarke R, Ritchie C, et al. Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. Lancet Neurol. 2008 Aug;7(8):683–9.

90. Starfield B, Hyde J, Gérvas J, Heath I. The concept of prevention: a good idea gone astray? J Epidemiol Community Health. 2008 Jul 1;62(7):580–3.

91. Spatz ES, Krumholz HM, Moulton BW. Prime Time for Shared Decision Making. JAMA. 2017 04;317(13):1309–10.

92. Harrison M, Milbers K, Hudson M, Bansback N. Do patients and health care providers have discordant preferences about which aspects of treatments matter most? Evidence from a systematic review of discrete choice experiments. BMJ Open. 2017 May 1;7(5):e014719.

93. Stacey D, Légaré F, Lewis K, Barry MJ, Bennett CL, Eden KB, et al. Decision aids for people facing health treatment or screening decisions. Cochrane Database Syst Rev. 2017 Apr 12;4:CD001431.

94. Jansen J, Naganathan V, Carter SM, McLachlan AJ, Nickel B, Irwig L, et al. Too much medicine in older people? Deprescribing through shared decision making. BMJ. 2016 Jun 3;353:i2893.

95. Leung AA, Daskalopoulou SS, Dasgupta K, McBrien K, Butalia S, Zarnke KB, et al. Hypertension Canada's 2017 Guidelines for Diagnosis, Risk Assessment, Prevention, and Treatment of Hypertension in Adults. Canadian Journal of Cardiology. 2017 May 1;33(5):557–76.

96. Sussman JB, Kerr EA, Saini SD, et al. Rates of deintensification of blood pressure and glycemic medication treatment based on levels of control and life expectancy in older patients with diabetes mellitus. JAMA Intern Med. 2015 Oct 26;1–8.

97. McAlister FA, Youngson E, Eurich DT. Treatment Deintensification Is Uncommon in Adults With Type 2 Diabetes Mellitus: A Retrospective Cohort Study. Circ Cardiovasc Qual Outcomes. 2017 Apr;10(4).

98. Moonen JEF, Foster-Dingley JC, de Ruijter W, van der Grond J, de Craen AJM, van der Mast RC. Effect of discontinuation of antihypertensive medication on orthostatic hypotension in older persons with mild cognitive impairment: the DANTE Study Leiden. Age Ageing. 2016 Jan 11;

99. Kolata G. Blood Pressure, the Mystery Number. 2015 Jul 23 [cited 2015 Aug 4]; Available from: http://www.nytimes.com/2015/06/23/health/blood-pressure-the-mystery-number.html

100. Group TSR. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. New England Journal of Medicine. 2015 Nov 26;373(22):2103–16.

101. Kolata G. Lower Blood Pressure Guidelines Could Be 'Lifesaving,' Federal Study Says. The New York Times [Internet]. 2015 Sep 11 [cited 2015 Oct 11]; Available from: http://www.nytimes.com/2015/09/12/health/blood-pressure-study.html

102. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ. 2009 May 19;338:b1665.

103. Cavero-Redondo I, Peleteiro B, Álvarez-Bueno C, Rodriguez-Artalejo F, Martínez-Vizcaíno V. Glycated haemoglobin A1c as a risk factor of cardiovascular outcomes and all-cause mortality in diabetic and non-diabetic populations: a systematic review and meta-analysis. BMJ Open. 2017 Jul 31;7(7):e015949.

104. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R, Prospective Studies Collaboration. 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 Dec 14;360(9349):1903–13.

105. Kearney PM, Whelton M, Reynolds K, Whelton PK, He J. Worldwide prevalence of hypertension: a systematic review. J Hypertens. 2004 Jan;22(1):11–9.

106. Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19·1 million participants. The Lancet. 2017 Jan 7;389(10064):37–55.

107. Padwal RS, Bienek A, McAlister FA, Campbell NRC. Epidemiology of Hypertension in Canada: An Update. Canadian Journal of Cardiology. 2016 May;32(5):687–94.

108. Godwin M, Williamson T, Khan S, Kaczorowski J, Asghari S, Morkem R, et al. Prevalence and management of hypertension in primary care practices with electronic medical records: a report from the Canadian Primary Care Sentinel Surveillance Network. CMAJ Open. 2015 Feb 25;3(1):E76–82.

109. Robitaille C, Dai S, Waters C, Loukine L, Bancej C, Quach S, et al. Diagnosed hypertension in Canada: incidence, prevalence and associated mortality. CMAJ. 2012 Jan 10;184(1):E49–56.

110. Egan BM, Li J, Shatat IF, Fuller JM, Sinopoli A. Closing the gap in hypertension control between younger and older adults: National Health and Nutrition Examination Survey (NHANES) 1988 to 2010. Circulation. 2014 May 20;129(20):2052–61.

111. Ravindrarajah R, Hazra NC, Hamada S, Charlton J, Jackson SHD, Dregan A, et al. Systolic Blood Pressure Trajectory, Frailty and All-Cause Mortality Over 80 Years of Age. Cohort Study Using Electronic Health Records. Circulation. 2017 Apr 21;

112. Clegg A, Bates C, Young J, Ryan R, Nichols L, Teale EA, et al. Development and validation of an electronic frailty index using routine primary care electronic health record data. Age Ageing. 2017 Jan 17;

113. Kang M-G, Kim S-W, Yoon S-J, Choi J-Y, Kim K-I, Kim C-H. Association between Frailty and Hypertension Prevalence, Treatment, and Control in the Elderly Korean Population. Sci Rep. 2017 Aug 8;7(1):7542.

114. Hypertension Canada. IV. Ambulatory BP Measurement | CHEP Guidelines [Internet]. Hypertension Canada. 2017 [cited 2017 Nov 1]. Available from: http://guidelines.hypertension.ca/diagnosis-assessment/ambulatory-measurement/

115. Rapsomaniki E, Timmis A, George J, Pujades-Rodriguez M, Shah AD, Denaxas S, et al. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1·25 million people. Lancet. 2014 May 31;383(9932):1899–911.

116. Musini VM, Tejani AM, Bassett K, Wright JM. Pharmacotherapy for hypertension in the elderly. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD000028.

117. Bejan-Angoulvant T, Saadatian-Elahi M, Wright JM, Schron EB, Lindholm LH, Fagard R, et al. Treatment of hypertension in patients 80 years and older: the lower the better? A meta-analysis of randomized controlled trials. J Hypertens. 2010 Jul;28(7):1366–72.

118. 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). Clinical Trials. 2014 Oct 1;11(5):532–46.

119. Weiss J, Freeman M, Low A, Fu R, Kerfoot A, Paynter R, et al. Benefits and Harms of Intensive Blood Pressure Treatment in Adults Aged 60 Years or Older: A Systematic Review and Meta-analysis. Ann Intern Med. 2017 Mar 21;166(6):419–29.

120. Garrison SR, Kolber MR, Korownyk CS, McCracken RK, Heran BS, Allan GM. Blood pressure targets for hypertension in older adults. Cochrane Database Syst Rev. 2017 08;8:CD011575.

121. Guyatt GH, Sackett DL, Sinclair JC, Hayward R, Cook DJ, Cook RJ. Users' guides to the medical literature. IX. A method for grading health care recommendations. Evidence-Based Medicine Working Group. JAMA. 1995 Dec 13;274(22):1800–4.

122. Scott IA, Guyatt GH. Cautionary tales in the interpretation of clinical studies involving older persons. Arch Intern Med. 2010 Apr 12;170(7):587–95.

123. Davies K, Collerton JC, Jagger C, Bond J, Barker SAH, Edwards J, et al. Engaging the oldest old in research: lessons from the Newcastle 85+ study. BMC Geriatr. 2010 Sep 17;10:64.

124. Sinclair H, Batty JA, Qiu W, Kunadian V. Engaging older patients in cardiovascular research: observational analysis of the ICON-1 study. Open Heart. 2016;3(2):e000436.

125. Downing NS, Shah ND, Neiman JH, Aminawung JA, Krumholz HM, Ross JS. Participation of the elderly, women, and minorities in pivotal trials supporting 2011-2013 U.S. Food and Drug Administration approvals. Trials. 2016 Apr 14;17:199.

126. Taylor JS, DeMers SM, Vig EK, Borson S. The disappearing subject: exclusion of people with cognitive impairment and dementia from geriatrics research. J Am Geriatr Soc. 2012 Mar;60(3):413–9.

127. Seegers V, Trinquart L, Boutron I, Ravaud P. Comparison of treatment effect estimates for pharmacological randomized controlled trials enrolling older adults only and those including adults: a meta-epidemiological study. PLoS ONE. 2013;8(5):e63677.

128. Liu L, Zhang Y, Liu G, Li W, Zhang X, Zanchetti A, et al. The Felodipine Event Reduction (FEVER) Study: a randomized long-term placebo-controlled trial in Chinese hypertensive patients. J Hypertens. 2005 Dec;23(12):2157–72.

129. JATOS Study Group. The Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients (JATOS): protocol, patient characteristics, and blood pressure during the first 12 months. Hypertens Res. 2005 Jun;28(6):513–20.

130. Ogihara T, Saruta T, Rakugi H, Matsuoka H, Shimamoto K, Shimada K, et al. Target blood pressure for treatment of isolated systolic hypertension in the elderly: valsartan in elderly isolated systolic hypertension study. Hypertension. 2010 Aug;56(2):196–202.

131. Wei Y, Jin Z, Shen G, Zhao X, Yang W, Zhong Y, et al. Effects of intensive antihypertensive treatment on Chinese hypertensive patients older than 70 years. J Clin Hypertens (Greenwich). 2013 Jun;15(6):420–7.

132. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med. 1999 Sep 2;341(10):709–17.

133. Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A, et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. N Engl J Med. 2004 Aug 5;351(6):543–51.

134. Lim E, Brown A, Helmy A, Mussa S, Altman DG. Composite outcomes in cardiovascular research: a survey of randomized trials. Ann Intern Med. 2008 Nov 4;149(9):612–7.

135. Ferreira-González I, Busse JW, Heels-Ansdell D, Montori VM, Akl EA, Bryant DM, et al. Problems with use of composite end points in cardiovascular trials: systematic review of randomised controlled trials. BMJ. 2007 Apr 14;334(7597):786.

136. Reuben DB, Tinetti ME. Goal-Oriented Patient Care — An Alternative Health Outcomes Paradigm. New England Journal of Medicine. 2012 Mar 1;366(9):777–9.

137. Golder S, Loke YK, Wright K, Norman G. Reporting of Adverse Events in Published and Unpublished Studies of Health Care Interventions: A Systematic Review. PLOS Medicine. 2016 Sep 20;13(9):e1002127.

138. Bagul NB, Kirkham JJ. The reporting of harms in randomized controlled trials of hypertension using the CONSORT criteria for harm reporting. Clin Exp Hypertens. 2012;34(8):548–54.

139. Moher D. CONSORT: An Evolving Tool to Help Improve the Quality of Reports of Randomized Controlled Trials. JAMA. 1998 May 13;279(18):1489–91.

140. Frieden TR. Evidence for Health Decision Making - Beyond Randomized, Controlled Trials. N Engl J Med. 2017 03;377(5):465–75.

141. Miles A, Loughlin M. Models in the balance: evidence-based medicine versus evidence-informed individualized care. J Eval Clin Pract. 2011 Aug;17(4):531–6.

142. Tricoci P, Allen JM, Kramer JM, Califf RM, Smith SC. Scientific evidence underlying the ACC/AHA clinical practice guidelines. JAMA. 2009 Feb 25;301(8):831–41.

143. Allan GM, Kraut R, Crawshay A, Korownyk C, Vandermeer B, Kolber MR. Contributors to primary care guidelines What are their professions and how many of them have conflicts of interest? Can Fam Physician. 2015 Jan 1;61(1):52–8.

144. Jansen J, McKinn S, Bonner C, Irwig L, Doust J, Glasziou P, et al. Systematic review of clinical practice guidelines recommendations about primary cardiovascular disease prevention for older adults. BMC Fam Pract [Internet]. 2015 Aug 20;16. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4546022/

145. Mutasingwa DR, Ge H, Upshur REG. How applicable are clinical practice guidelines to elderly patients with comorbidities? Can Fam Physician. 2011 Jul;57(7):e253–62.

146. Onder G, Landi F, Fusco D, Corsonello A, Tosato M, Battaglia M, et al. Recommendations to prescribe in complex older adults: results of the CRIteria to assess appropriate Medication use among Elderly complex patients (CRIME) project. Drugs Aging. 2014 Jan;31(1):33–45.

147. Wolf-Maier K, Cooper RS, Kramer H, Banegas JR, Giampaoli S, Joffres MR, et al. Hypertension Treatment and Control in Five European Countries, Canada, and the United States. Hypertension. 2004 Jan 1;43(1):10–7.

148. Parekh N, Page A, Ali K, Davies K, Rajkumar C. A practical approach to the pharmacological management of hypertension in older people. Ther Adv Drug Saf. 2017 Apr;8(4):117–32.

149. Mancia G, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens. 2013 Jul;31(7):1281–357.

150. National Institute for Health and Clinical Excellence (NICE). Hypertension in adults: diagnosis and management. NICE Guideline (CG127) [Internet]. 2011 [cited 2017 Oct 26]. Available from: https://www.nice.org.uk/guidance/cg127

151. Weber MA, Schiffrin EL, White WB, Mann S, Lindholm LH, Kenerson JG, et al. Clinical practice guidelines for the management of hypertension in the community: a statement by the American Society of Hypertension and the International Society of Hypertension. J Clin Hypertens (Greenwich). 2014 Jan;16(1):14–26.

152. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014 Feb 5;311(5):507–20.

153. Benetos A, Bulpitt CJ, Petrovic M, Ungar A, Rosei EA, Cherubini A, et al. An Expert Opinion From the European Society of Hypertension–European Union Geriatric Medicine Society Working Group on the Management of Hypertension in Very Old, Frail Subjects. Hypertension. 2016 May 1;67(5):820–5.

154. Lu J, Lu Y, Wang X, Li X, Linderman GC, Wu C, et al. Prevalence, awareness, treatment, and control of hypertension in China: data from 1·7 million adults in a population-based screening study (China PEACE Million Persons Project). The Lancet [Internet]. 2017 Oct 25 [cited 2017 Oct 30];0(0). Available from: http://thelancet.com/journals/lancet/article/PIIS0140-6736(17)32478-9/abstract

155. Bromfield SG, Bowling CB, Tanner RM, Peralta CA, Odden MC, Oparil S, et al. Trends in hypertension prevalence, awareness, treatment, and control among US adults 80 years and older, 1988-2010. J Clin Hypertens (Greenwich). 2014 Apr;16(4):270–6.

156. Lindblad AJ, Makowsky M, Allan GM. Treating to target: ready, fire, aim. Can Fam Physician. 2014 Jun 1;60(6):541–541.

157. Chowdhury EK, Owen A, Krum H, Wing LMH, Ryan P, Nelson MR, et al. Barriers to achieving blood pressure treatment targets in elderly hypertensive individuals. J Hum Hypertens. 2013 Sep;27(9):545–51.

158. Collerton J, Barrass K, Bond J, Eccles M, Jagger C, James O, et al. The Newcastle 85+ study: biological, clinical and psychosocial factors associated with healthy ageing: study protocol. BMC Geriatr. 2007 Jun 26;7:14.

159. Boshuizen HC, Izaks GJ, Buuren S van, Ligthart GJ. Blood pressure and mortality in elderly people aged 85 and older: community based study. BMJ : British Medical Journal. 1998 Jun 13;316(7147):1780.

160. von Heideken Wågert P, Gustavsson JM, Lundin-Olsson L, Kallin K, Nygren B, Lundman B, et al. Health status in the oldest old. Age and sex differences in the Umeå 85+ Study. Aging Clin Exp Res. 2006 Apr;18(2):116–26.

161. Ogliari G, Westendorp RGJ, Muller M, Mari D, Torresani E, Felicetta I, et al. Blood pressure and 10-year mortality risk in the Milan Geriatrics 75+ Cohort Study: role of functional and cognitive status. Age Ageing. 2015 Nov;44(6):932–7.

162. Poortvliet RKE, de Ruijter W, de Craen AJM, Mooijaart SP, Westendorp RGJ, Assendelft WJJ, et al. Blood pressure trends and mortality: the Leiden 85-plus Study. J Hypertens. 2013 Jan;31(1):63–70.

163. Morrissey Y, Bedford M, Irving J, Farmer CKT. Older people remain on blood pressure agents despite being hypotensive resulting in increased mortality and hospital admission. Age Ageing. 2016 Nov;45(6):783–8.

164. Shih C-J, Chen Y-T, Ou S-M, Lin C-H, Tarng D-C. Observed Blood Pressure and Mortality Among People Aged 65 Years and Older: A Community-Based Cohort Study. Journal of the American Medical Directors Association [Internet]. [cited 2016 May 23]; Available from: http://www.sciencedirect.com/science/article/pii/S1525861016300901

165. Odden MC, Peralta CA, Haan MN, Covinsky KE. Rethinking the association of high blood pressure with mortality in elderly adults: the impact of frailty. Arch Intern Med. 2012 Aug 13;172(15):1162–8.

166. Chambers L, Bancej C, McDowell I. Prevalence and Monetary Costs of Dementia in Canada [Internet]. Toronto, ON: Alzheimer's Society of Canada; 2016 [cited 2017 Aug 2]. Available from: http://www.alzheimer.ca/~/media/Files/national/Statistics/PrevalenceandCostsofDementia_EN.pdf

167. Yasar S, Schuchman M, Peters J, Anstey KJ, Carlson MC, Peters R. Relationship Between Antihypertensive Medications and Cognitive Impairment: Part I. Review of Human Studies and Clinical Trials. Curr Hypertens Rep. 2016 Aug;18(8):67.

168. Jongstra S, Harrison JK, Quinn TJ, Richard E. Antihypertensive withdrawal for the prevention of cognitive decline. Cochrane Database Syst Rev. 2016 Nov 1;11:CD011971.

169. Power MC, Weuve J, Gagne JJ, McQueen MB, Viswanathan A, Blacker D. The association between blood pressure and incident Alzheimer disease: a systematic review and meta-analysis. Epidemiology. 2011 Sep;22(5):646–59.

170. Shah K, Qureshi SU, Johnson M, Parikh N, Schulz PE, Kunik ME. Does use of antihypertensive drugs affect the incidence or progression of dementia? A systematic review. Am J Geriatr Pharmacother. 2009 Oct;7(5):250–61.

171. McGuinness B, Todd S, Passmore P, Bullock R. Blood pressure lowering in patients without prior cerebrovascular disease for prevention of cognitive impairment and dementia. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD004034.

172. Kennelly SP, Lawlor BA, Kenny RA. Blood Pressure and Dementia – a Comprehensive Review. Ther Adv Neurol Disord. 2009 Jul;2(4):241–60.

173. Qiu C, Winblad B, Fratiglioni L. The age-dependent relation of blood pressure to cognitive function and dementia. The Lancet Neurology. 2005 Aug;4(8):487–99.

174. Rouch L, Cestac P, Hanon O, Cool C, Helmer C, Bouhanick B, et al. Antihypertensive Drugs, Prevention of Cognitive Decline and Dementia: A Systematic Review of Observational Studies, Randomized Controlled Trials and Meta-Analyses, with Discussion of Potential Mechanisms. CNS Drugs. 2015 Feb 21;29(2):113–30.

175. NIH (National Heart Lung and Blood Institute). Systolic Blood Pressure Intervention Trial (SPRINT) OVERVIEW [Internet]. US Dept. of Health and Human Services. 2017 [cited 2018 May 28]. Available from: https://www.nhlbi.nih.gov/news/systolic-blood-pressure-intervention-trial-sprint-overview

176. Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, et al. Treatment of hypertension in patients 80 years of age or older. N Engl J Med. 2008 May 1;358:1887–98.

177. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: Final results of the systolic hypertension in the elderly program (shep). JAMA. 1991 Jun 26;265(24):3255–64.

178. Staessen JA, Fagard R, Thijs L, Celis H, Arabidze GG, Birkenhäger WH, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Lancet. 1997 Sep 13;350(9080):757–64.

179. Lithell H, Hansson L, Skoog I, Elmfeldt D, Hofman A, Olofsson B, et al. The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. J Hypertens. 2003 May;21(5):875–86.

180. Bronskill SE, Gill SS, Paterson JM, Bell CM, Anderson GM, Rochon PA. Exploring variation in rates of polypharmacy across long term care homes. J Am Med Dir Assoc. 2012 Mar;13(3):309.e15-21.

181. Fortin M, Hudon C, Haggerty J, van den Akker M, Almirall J. Prevalence estimates of multimorbidity: a comparative study of two sources. BMC Health Services Research. 2010 May 6;10:111.

182. Sinnott C, Bradley CP. Multimorbidity or polypharmacy: two sides of the same coin? Journal of Comorbidity. 2015 Apr 24;5(1):29–31.

183. Poudel A, Peel NM, Nissen LM, Mitchell CA, Gray LC, Hubbard RE. Adverse Outcomes in Relation to Polypharmacy in Robust and Frail Older Hospital Patients. J Am Med Dir Assoc. 2016 Jun 30;

184. Page AT, Potter K, Clifford R, Etherton-Beer C. Deprescribing in older people. Maturitas. 2016 Sep;91:115–34.

185. Johansson T, Abuzahra ME, Keller S, Mann E, Faller B, Sommerauer C, et al. Impact of strategies to reduce polypharmacy on clinically relevant endpoints: a systematic review and meta-analysis. Br J Clin Pharmacol. 2016 Aug 1;82(2):532–48.

186. Jokanovic N, Tan ECK, Dooley MJ, Kirkpatrick CM, Bell JS. Prevalence and Factors Associated With Polypharmacy in Long-Term Care Facilities: A Systematic Review. J Am Med Dir Assoc. 2015 Jun 1;16(6):535.e1-535.e12.

187. General Practice Services Committee, Doctors of BC and the BC Ministry of Health. Incentive Program Fees | GPSC [Internet]. General Practice Incentive Program Fees. [cited 2015 Jul 16]. Available from: http://www.gpscbc.ca/billing-fees/incentive-program-fees

188. Maclure M, Dormuth C, Naumann T, McCormack J, Rangno R, Whiteside C, et al. Influences of educational interventions and adverse news about calcium-channel blockers on first-line prescribing of antihypertensive drugs to elderly people in British Columbia. The Lancet. 1998 Sep;352(9132):943–8.

189. McGregor M, Pare D, Wong A, Cox MB, Brasher P. Correlates of a “do not hospitalize” designation: In a sample of frail nursing home residents in Vancouver. Canadian Family Physician. 2010 Nov;56(11):1158.

190. Lipska KJ, Krumholz H, Soones T, Lee SJ. Polypharmacy in the aging patient: A review of glycemic control in older adults with type 2 diabetes. JAMA. 2016 Mar 8;315(10):1034–45.

191. Mossello E, Pieraccioli M, Nesti N, Bulgaresi M, Lorenzi C, Caleri V, et al. Effects of low blood pressure in cognitively impaired elderly patients treated with antihypertensive drugs. JAMA Intern Med. 2015 Apr;175(4):578–85.

192. Levy PS, Lemeshow S. Sampling of populations: methods and applications. 4th ed. Hoboken, N.J: Wiley; 2008. 1 p. (Wiley series in survey methodology).

193. Lipska KJ, Ross JS, Miao Y, Shah ND, Lee SJ, Steinman MA. Potential overtreatment of diabetes mellitus in older adults with tight glycemic control. JAMA Intern Med. 2015 Mar;175(3):356–62.

194. Tamura BK, Bell CL, Inaba M, Masaki KH. Factors associated with polypharmacy in nursing home residents. Clin Geriatr Med. 2012 May;28(2):199–216.

195. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, Meneilly GS, Knip A, Tessier D. Diabetes in the elderly. Can J Diabetes. 2013 Apr;37 Suppl 1:S184-190.

196. Daskalopoulou SS, Rabi DM, Zarnke KB, Dasgupta K, Nerenberg K, Cloutier L, et al. The 2015 Canadian Hypertension Education Program Recommendations for Blood Pressure Measurement, Diagnosis, Assessment of Risk, Prevention, and Treatment of Hypertension. Canadian Journal of Cardiology. 2015 May 1;31(5):549–68.

197. Proulx J, Hunt J. Drug Use among Seniors on Public Drug Programs in Canada, 2012. Healthcare Quarterly. 2015 Apr 30;18(1):11–3.

198. Alhawassi TM, Krass I, Bajorek BV, Pont LG. A systematic review of the prevalence and risk factors for adverse drug reactions in the elderly in the acute care setting. Clin Interv Aging. 2014;9:2079–86.

199. Lu W-H, Wen Y-W, Chen L-K, Hsiao F-Y. Effect of polypharmacy, potentially inappropriate medications and anticholinergic burden on clinical outcomes: a retrospective cohort study. CMAJ. 2015 Mar 3;187(4):E130–7.

200. Vidal-Petiot E, Ford I, Greenlaw N, Ferrari R, Fox KM, Tardif J-C, et al. Cardiovascular event rates and mortality according to achieved systolic and diastolic blood pressure in patients with stable coronary artery disease: an international cohort study. The Lancet. 2016 Nov 4;388(10056):2142–52.

201. Thake M, Lowry A. A systematic review of trends in the selective exclusion of older participant from randomised clinical trials. Archives of Gerontology and Geriatrics. 2017 Sep 1;72:99–102.

202. Dwan K, Altman DG, Arnaiz JA, Bloom J, Chan A-W, Cronin E, et al. Systematic Review of the Empirical Evidence of Study Publication Bias and Outcome Reporting Bias. PLOS ONE. 2008 Aug 28;3(8):e3081.

203. The SPRINT Research Group. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. New England Journal of Medicine. 2015 Nov 26;373(22):2103–16.

204. IV. Global Vascular Protection Therapy for Adults with Hypertension without Compelling Indications for Specific Agents | Hypertension Canada Guidelines [Internet]. [cited 2018 Mar 3]. Available from: http://guidelines.hypertension.ca/prevention-treatment/uncomplicated-hypertension-vascular-protection/

205. Queenan JA, Williamson T, Khan S, Drummond N, Garies S, Morkem R, et al. Representativeness of patients and providers in the Canadian Primary Care Sentinel Surveillance Network: a cross-sectional study. CMAJ Open. 2016 Mar;4(1):E28-32.

206. Williamson T, Green ME, Birtwhistle R, Khan S, Garies S, Wong ST, et al. Validating the 8 CPCSSN case definitions for chronic disease surveillance in a primary care database of electronic health records. Ann Fam Med. 2014 Jul;12(4):367–72.

207. Guidelines for ATC classification and DDD assignment. Oslo: WHO Collaborating Centre for Drug Statistics Methodology; 2016.

208. Williamson T. CPCSSN Disease Definitions: Canadian Primary Care Sentinel Surveillance Network (CPCSSN). 2014 Jun 14; Available from: http://cpcssn.ca/wp-content/uploads/.../CPCSSN_DiseaseDefinitionsFINAL_July16-2014.pdf

209. Alhawassi TM, Krass I, Pont LG. Hypertension in Older Persons: A Systematic Review of National and International Treatment Guidelines. J Clin Hypertens. 2015 Jun 1;17(6):486–92.

210. Webb AJ, Fischer U, Mehta Z, Rothwell PM. Effects of antihypertensive-drug class on interindividual variation in blood pressure and risk of stroke: a systematic review and meta-analysis. The Lancet. 2010 Mar;375(9718):906–15.

211. WHO Collaborating Centre for Drug Statistics Methodology, Guidelines for ATC classification and DDD assignment. 2016. Oslo, 2016. 2016.

212. Lipsitz LA, Habtemariam D, Gagnon M, Iloputaife I, Sorond F, Tchalla AE, et al. Reexamining the Effect of Antihypertensive Medications on Falls in Old Age. Hypertension. 2015 Jul;66(1):183–9.

213. Rothwell PM. Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension. The Lancet. 2010 Mar;375(9718):938–48.

214. Divisón-Garrote JA, Ruilope LM, Sierra A de la, Cruz JJ de la, Vinyoles E, Gorostidi M, et al. Magnitude of Hypotension Based on Office and Ambulatory Blood Pressure Monitoring: Results From a Cohort of 5066 Treated Hypertensive Patients Aged 80 Years and Older. Journal of the American Medical Directors Association [Internet]. 2017 Feb 26 [cited 2017 Mar 12];0(0). Available from: http://www.jamda.com/article/S1525-8610(17)30062-2/fulltext

215. Danaei G, Finucane MM, Lin JK, Singh GM, Paciorek CJ, Cowan MJ, et al. National, regional, and global trends in systolic blood pressure since 1980: systematic analysis of health examination surveys and epidemiological studies with 786 country-years and 5·4 million participants. Lancet. 2011 Feb 12;377(9765):568–77.

216. Gheorghiade M, Abraham WT, Albert NM, Greenberg BH, O'Connor CM, She L, et al. Systolic Blood Pressure at Admission, Clinical Characteristics, and Outcomes in Patients Hospitalized With Acute Heart Failure. JAMA. 2006 Nov 8;296(18):2217–26.

217. Szewczyk-Krolikowski K, Tomlinson P, Nithi K, Wade-Martins R, Talbot K, Ben-Shlomo Y, et al. The influence of age and gender on motor and non-motor features of early Parkinson's disease: initial findings from the Oxford Parkinson Disease Center (OPDC) discovery cohort. Parkinsonism Relat Disord. 2014 Jan;20(1):99–105.

218. Smith T, Maidment I, Hebding J, Madzima T, Cheater F, Cross J, et al. Systematic review investigating the reporting of comorbidities and medication in randomized controlled trials of people with dementia. Age Ageing. 2014 Nov;43(6):868–72.

219. Hildrum B, Mykletun A, Stordal E, Bjelland I, Dahl AA, Holmen J. Association of low blood pressure with anxiety and depression: the Nord-Trøndelag Health Study. J Epidemiol Community Health. 2007 Jan;61(1):53–8.

220. Buffel du Vaure C, Ravaud P, Baron G, Barnes C, Gilberg S, Boutron I. Potential workload in applying clinical practice guidelines for patients with chronic conditions and multimorbidity: a systematic analysis. BMJ Open. 2016 Mar 22;6(3):e010119.

221. Molander L, Lövheim H, Norman T, Nordström P, Gustafson Y. Lower systolic blood pressure is associated with greater mortality in people aged 85 and older. J Am Geriatr Soc. 2008 Oct;56(10):1853–9.

222. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. Journal of Chronic Diseases. 1987;40(5):373–83.

223. Crooks CJ, West J, Card TR. A comparison of the recording of comorbidity in primary and secondary care by using the Charlson Index to predict short-term and long-term survival in a routine linked data cohort. BMJ Open. 2015 Jun 1;5(6):e007974.

224. Starfield B, Lemke KW, Bernhardt T, Foldes SS, Forrest CB, Weiner JP. Comorbidity: Implications for the Importance of Primary Care in 'Case' Management. Ann Fam Med. 2003 May 1;1(1):8–14.

225. Hu T, Dattani ND, Cox KA, Au B, Xu L, Melady D, et al. Effect of comorbidities and medications on frequency of primary care visits among older patients. Can Fam Physician. 2017 Jan;63(1):45–50.

226. Stevens SL, Wood S, Koshiaris C, Law K, Glasziou P, Stevens RJ, et al. Blood pressure variability and cardiovascular disease: systematic review and meta-analysis. BMJ. 2016 Aug 9;354:i4098.

227. Mancia G. Short- and Long-Term Blood Pressure Variability Present and Future. Hypertension. 2012 Aug 1;60(2):512–7.

228. Mancia G, Bombelli M, Facchetti R, Madotto F, Corrao G, Trevano FQ, et al. Long-Term Prognostic Value of Blood Pressure Variability in the General Population Results of the Pressioni Arteriose Monitorate e Loro Associazioni Study. Hypertension. 2007 Jun 1;49(6):1265–70.

229. Kikuya M, Ohkubo T, Metoki H, Asayama K, Hara A, Obara T, et al. Day-by-Day Variability of Blood Pressure and Heart Rate at Home as a Novel Predictor of Prognosis The Ohasama Study. Hypertension. 2008 Dec 1;52(6):1045–50.

230. Malek Makan A, van Hout H, Onder G, Finne-Soveri H, van der Roest H, van Marum R. Prevalence of Preventive Cardiovascular Medication Use In Nursing Home Residents. Room for Deprescribing? The SHELTER Study. J Am Med Dir Assoc. 2017 Sep 1;

231. Benetos A, Rossignol P, Cherubini A, et al. Polypharmacy in the aging patient: Management of hypertension in octogenarians. JAMA. 2015 Jul 14;314(2):170–80.

232. Fortin M, Dionne J, Pinho G, Gignac J, Almirall J, Lapointe L. Randomized controlled trials: do they have external validity for patients with multiple comorbidities? Ann Fam Med. 2006 Apr;4(2):104–8.

233. Hammer GP, du Prel J-B, Blettner M. Avoiding Bias in Observational Studies. Dtsch Arztebl Int. 2009 Oct;106(41):664–8.

234. Singer A, Kroeker AL, Yakubovich S, Duarte R, Dufault B, Katz A. Data quality in electronic medical records in Manitoba: Do problem lists reflect chronic disease as defined by prescriptions? Can Fam Physician. 2017 May;63(5):382–9.

235. Therapeutics Initiative. [98] Does SPRINT change our approach to blood pressure targets? Therapeutics Letter. 2016 Apr 7;98:2.

236. Gurwitz JH, Goldberg RJ. Age-based exclusions from cardiovascular clinical trials: implications for elderly individuals (and for all of us): comment on “the persistent exclusion of older patients from ongoing clinical trials regarding heart failure.” Arch Intern Med. 2011 Mar 28;171(6):557–8.

237. Bari MD, Pahor M, Franse LV, Shorr RI, Wan JY, Ferrucci L, et al. Dementia and Disability Outcomes in Large Hypertension Trials: Lessons Learned from the Systolic Hypertension in the Elderly Program (SHEP) Trial. Am J Epidemiol. 2001 Jan 1;153(1):72–8.

238. Sabayan B, Westendorp RGJ. Blood pressure control and cognitive impairment--why low is not always better. JAMA Intern Med. 2015 Apr;175(4):586–7.

239. Drummond N, Birtwhistle R, Williamson T, Khan S, Garies S, Molnar F. Prevalence and management of dementia in primary care practices with electronic medical records: a report from the Canadian Primary Care Sentinel Surveillance Network. cmajo. 2016 Apr 28;4(2):E177–84.

240. Beevers G, Lip GYH, O'Brien E. Blood pressure measurement. BMJ. 2001 Apr 21;322(7292):981–5.

241. Zhou Z, Rahme E, Abrahamowicz M, Pilote L. Survival Bias Associated with Time-to-Treatment Initiation in Drug Effectiveness Evaluation: A Comparison of Methods. Am J Epidemiol. 2005 Nov 15;162(10):1016–23.

242. Hong SH, Wang J, Tak S. A patient-centric goal in time to blood pressure control from drug therapy initiation. Clin Transl Sci. 2013 Feb;6(1):7–12.

243. Skoog I, Lernfelt B, Landahl S, Palmertz B, Andreasson LA, Nilsson L, et al. 15-year longitudinal study of blood pressure and dementia. Lancet. 1996 Apr 27;347(9009):1141–5.

244. Banach M, Aronow WS. Blood Pressure J-Curve: Current Concepts. Current Hypertension Reports. 2012 Dec;14(6):556–66.

245. Malyszko J, Muntner P, Rysz J, Banach M. Blood Pressure Levels and Stroke: J-curve Phenomenon? Current Hypertension Reports. 2013 Dec;15(6):575–81.

246. Alpérovitch A, Blachier M, Soumaré A, Ritchie K, Dartigues J-F, Richard-Harston S, et al. Blood pressure variability and risk of dementia in an elderly cohort, the Three-City Study. Alzheimer's & Dementia. 2014 Oct;10(5, Supplement):S330–7.

247. Crichton GE, Elias MF, Dore GA, Torres RV, Robbins MA. Measurement-to-measurement blood pressure variability is related to cognitive performance: the Maine Syracuse study. Hypertension. 2014 Nov;64(5):1094–101.

248. Tully PJ, Dartigues J-F, Debette S, Helmer C, Artero S, Tzourio C. Dementia risk with antihypertensive use and blood pressure variability: A cohort study. Neurology. 2016 Aug 9;87(6):601–8.

249. Baumgart M, Snyder HM, Carrillo MC, Fazio S, Kim H, Johns H. Summary of the evidence on modifiable risk factors for cognitive decline and dementia: A population-based perspective. Alzheimer's & Dementia: The Journal of the Alzheimer's Association. 2015 Jun 1;11(6):718–26.

250. Diniz BS, Butters MA, Albert SM, Dew MA, Reynolds CF 3rd. Late-life depression and risk of vascular dementia and Alzheimer's disease: systematic review and meta-analysis of community-based cohort studies. Br J Psychiatry. 2013 May;202(5):329–35.

251. Gray SL, Anderson ML, Dublin S, et al. Cumulative use of strong anticholinergics and incident dementia: A prospective cohort study. JAMA Intern Med. 2015 Mar 1;175(3):401–7.

252. Tonelli M, Wiebe N, Straus S, Fortin M, Guthrie B, James MT, et al. Multimorbidity, dementia and health care in older people:a population-based cohort study. CMAJ Open. 2017 Aug 14;5(3):E623–31.

253. Oishi E, Ohara T, Sakata S, Fukuhara M, Hata J, Yoshida D, et al. Day-to-Day Blood Pressure Variability and Risk of Dementia in a General Japanese Elderly Population: The Hisayama Study. Circulation. 2017 Aug 8;136(6):516–25.

254. Brilleman SL, Salisbury C. Comparing measures of multimorbidity to predict outcomes in primary care: a cross sectional study. Fam Pract. 2013 Apr;30(2):172–8.

255. Zhao Y, Wright J, Guthridge S, Lawton P. The relationship between number of primary health care visits and hospitalisations: evidence from linked clinic and hospital data for remote Indigenous Australians. BMC Health Serv Res. 2013 Nov 6;13:466.

256. Yurkovich M, Avina-Zubieta JA, Thomas J, Gorenchtein M, Lacaille D. A systematic review identifies valid comorbidity indices derived from administrative health data. J Clin Epidemiol. 2015 Jan;68(1):3–14.

257. George B, Seals S, Aban I. Survival analysis and regression models. J Nucl Cardiol. 2014 Aug;21(4):686–94.

258. Garson GD. Cox Regression [Internet]. Kindle Edition. G. David Garson and Statistical Associates Publishing.; 2013 [cited 2017 Jun 21]. (Blue Book Series). Available from: http://www.statisticalassociates.com/coxregression.htm

259. Dudley,1 WN, Wickham,2 R, COOMBS,3 N. An Introduction to Survival Statistics: Kaplan-Meier Analysis. J Adv Pract Oncol. 2016;7(1):91–100.

260. Forette F, Seux ML, Staessen JA, Thijs L, Birkenhäger WH, Babarskiene MR, et al. Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. Lancet. 1998 Oct 24;352(9137):1347–51.

261. Iadecola C, Yaffe K, Biller J, Bratzke LC, Faraci FM, Gorelick PB, et al. Impact of Hypertension on Cognitive Function: A Scientific Statement From the American Heart Association. Hypertension. 2016 Jan 1;HYP.0000000000000053.

262. Hajjar I, Rosenberger KJ, Kulshreshtha A, Ayonayon HN, Yaffe K, Goldstein FC. Association of JNC-8 and SPRINT Systolic Blood Pressure Levels With Cognitive Function and Related Racial Disparity. JAMA Neurol. 2017 Aug 21;

263. Tombaugh TN. Test-retest reliable coefficients and 5-year change scores for the MMSE and 3MS. Archives of Clinical Neuropsychology. 2005 Jun 1;20(4):485–503.

264. Andrew MK, Rockwood K. A five-point change in Modified Mini-Mental State Examination was clinically meaningful in community-dwelling elderly people. J Clin Epidemiol. 2008 Aug;61(8):827–31.

265. Jüni P, Egger M. Commentary: Empirical evidence of attrition bias in clinical trials. Int J Epidemiol. 2005 Feb 1;34(1):87–8.

266. Moonen JF, Foster-Dingley JC, de Ruijter W, et al. Effect of discontinuation of antihypertensive treatment in elderly people on cognitive functioning—the dante study

leiden: A randomized clinical trial. JAMA Intern Med [Internet]. 2015 Aug 24 [cited 2015 Aug 26]; Available from: http://dx.doi.org/10.1001/jamainternmed.2015.4103

267. Gottesman RF, Albert MS, Alonso A, Coker LH, Coresh J, Davis SM, et al. Associations Between Midlife Vascular Risk Factors and 25-Year Incident Dementia in the Atherosclerosis Risk in Communities (ARIC) Cohort. JAMA Neurol. 2017 Oct 1;74(10):1246–54.

268. Kennedy-Martin T, Curtis S, Faries D, Robinson S, Johnston J. A literature review on the representativeness of randomized controlled trial samples and implications for the external validity of trial results. Trials. 2015;16(1):495.

269. Cherubini A, Oristrell J, Pla X, Ruggiero C, Ferretti R, Diestre G, et al. The persistent exclusion of older patients from ongoing clinical trials regarding heart failure. Arch Intern Med. 2011 Mar 28;171(6):550–6.

270. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the Concepts of Disability, Frailty, and Comorbidity: Implications for Improved Targeting and Care. J Gerontol A Biol Sci Med Sci. 2004 Mar 1;59(3):M255–63.

271. Stawicki SP, Kalra S, Jones C, Justiniano CF, Papadimos TJ, Galwankar SC, et al. Comorbidity polypharmacy score and its clinical utility: A pragmatic practitioner's perspective. J Emerg Trauma Shock. 2015;8(4):224–31.

272. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlöf B, et al. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. The Lancet. 2010 Mar;375(9718):895–905.

273. Damluji AA, Ramireddy A, Otalvaro L, Forman DE. Secondary cardiovascular prevention in older adults: an evidence based review. J Geriatr Cardiol. 2015 Sep;12(5):459–64.

274. Austad B, Hetlevik I, Mjølstad BP, Helvik A-S. Applying clinical guidelines in general practice: a qualitative study of potential complications. BMC Family Practice. 2016;17:92.

275. Markovitz AA, Hofer TP, Froehlich W, Lohman SE, Caverly TJ, Sussman JB, et al. An Examination of Deintensification Recommendations in Clinical Practice Guidelines: Stepping Up or Scaling Back? JAMA Intern Med [Internet]. 2017 Dec 18 [cited 2018 Jan 3]; Available from: https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2665384

276. Kent DM, Hayward RA. Limitations of applying summary results of clinical trials to individual patients: the need for risk stratification. JAMA. 2007 Sep 12;298(10):1209–12.

277. van der Wardt V, Harrison JK, Welsh T, Conroy S, Gladman J. Withdrawal of antihypertensive medication: a systematic review. J Hypertens. 2017 Sep;35(9):1742–9.

278. Bakalar N. Blood Pressure? 120 May Be a Good Target. The New York Times [Internet]. 2017 Feb 15 [cited 2018 Apr 16]; Available from: https://www.nytimes.com/2017/02/15/well/live/blood-pressure-120-may-be-a-good-target.html

279. Warwick J, Falaschetti E, Rockwood K, Mitnitski A, Thijs L, Beckett N, et al. No evidence that frailty modifies the positive impact of antihypertensive treatment in very elderly people: an investigation of the impact of frailty upon treatment effect in the HYpertension in the Very Elderly Trial (HYVET) study, a double-blind, placebo-controlled study of antihypertensives in people with hypertension aged 80 and over. BMC Med. 2015;13:78.

280. Williamson JD, Supiano MA, Applegate WB, Berlowitz DR, Campbell RC, Chertow GM, et al. Intensive vs Standard Blood Pressure Control and Cardiovascular Disease Outcomes in Adults Aged ≥75 Years: A Randomized Clinical Trial. JAMA. 2016 Jun 28;315(24):2673–82.

281. Xie X, Atkins E, Lv J, Bennett A, Neal B, Ninomiya T, et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. The Lancet [Internet]. 2015 Nov [cited 2015 Dec 8]; Available from: http://linkinghub.elsevier.com/retrieve/pii/S0140673615008053

282. Wirtz HS, Calip GS, Buist DSM, Gralow JR, Barlow WE, Gray S, et al. Evidence for Detection Bias by Medication Use in a Cohort Study of Breast Cancer Survivors. Am J Epidemiol. 2017 Apr 15;185(8):661–72.

283. Sørensen HT, Sabroe S, Olsen J. A Framework for Evaluation of Secondary Data Sources for Epidemiological Research. Int J Epidemiol. 1996 Apr 1;25(2):435–42.

284. Dochi M, Sakata K, Oishi M, Tanaka K, Kobayashi E, Suwazono Y. Smoking as an independent risk factor for hypertension: a 14-year longitudinal study in male Japanese workers. Tohoku J Exp Med. 2009 Jan;217(1):37–43.

285. Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. Lancet Neurol. 2011 Sep;10(9):819–28.

286. Polubriaginof F, Salmasian H, Albert DA, Vawdrey DK. Challenges with Collecting Smoking Status in Electronic Health Records. AMIA Annu Symp Proc. 2018 Apr 16;2017:1392–400.

287. Szatkowski L, Lewis S, McNeill A, Coleman T. Is smoking status routinely recorded when patients register with a new GP? Fam Pract. 2010 Dec 1;27(6):673–5.

288. Kivipelto M, Helkala EL, Laakso MP, Hänninen T, Hallikainen M, Alhainen K, et al. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. BMJ. 2001 Jun 16;322(7300):1447–51.

289. Charlton J, Rudisill C, Bhattarai N, Gulliford M. Impact of deprivation on occurrence, outcomes and health care costs of people with multiple morbidity. J Health Serv Res Policy. 2013 Oct;18(4):215–23.

290. Cadar D, Lassale C, Davies H, Llewellyn DJ, Batty GD, Steptoe A. Individual and Area-Based Socioeconomic Factors Associated With Dementia Incidence in England: Evidence From a 12-Year Follow-up in the English Longitudinal Study of Ageing. JAMA Psychiatry. 2018 Jul 1;75(7):723–32.

291. McGregor MJ, Tate RB, McGrail KM, Ronald LA, Broemeling A-M, Cohen M. Care Outcomes in Long-Term Care Facilities in British Columbia, Canada: Does Ownership Matter? Medical Care. 2006 Oct 1;44(10):929–35.

292. Reboussin DM, Allen NB, Griswold ME, Guallar E, Hong Y, Lackland DT, et al. Systematic Review for the 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2017 Nov 13;