The health system costs of potentially inappropriate prescribing in Ontario: a population-based study

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Preface

Contributions of the student

Cody Black is the principal author of all thesis content. The concept and methods for the studies were conceived by Cody Black, Lise Bjerre, Kednapa Thavorn and Doug Coyle, and funding was secured by Lise Bjerre (CIHR Grant # 287245-HPM-BRUY-46830). Cohort creation, as well as exposure and outcome ascertainment, was conducted by Cody Black and Glenys Smith. Cody Black analyzed data with assistance from Kednapa Thavorn. The three manuscripts were written by Cody Black. All listed authors for each manuscript provided feedback and approval of the final versions presented within this thesis.

Approvals

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The studies conducted in Chapters 3 and 4 were approved by the institutional review board at Sunnybrook Health Sciences Centre, Toronto, Canada.

Abbreviations

ACE	angiotensin-converting-enzyme
ADE	adverse drug event
ADG	Aggregated Diagnosis Groups
ED	Emergency Department
GLM	generalized linear model
HAD	health administrative databases
ICES	Institute for Clinical Evaluative Sciences
OLS	ordinary least squares
PIO	potentially inappropriate omission
PIP	potentially inappropriate prescription
STOPP/START	screening tool of older people's prescriptions (STOPP) and screening tool to alert to right treatment (START)
95% CI	95% confidence interval

Abstract

Potentially Inappropriate Prescribing (PIP) is common in Canada yet little is known about its health system costs or which PIPs have the greatest cost impact. This thesis examined the health system costs from hospitalizations, emergency department (ED) visits and medications from all PIP, and for distinct PIP.

PIPs were identified in a cohort of older adults in Ontario using a subset of the STOPP/START criteria applicable to health administrative databases, and all analyses were conducted by comparing participants with and without PIP. In study one, the costs from hospitalization, ED visits and newly prescribed medications were identified using population attributable fractions. PIP was identified as responsible for a sizeable portion of all three cost categories, with hospitalization and ED visits costs most highly impacted. Study two compared the incremental costs due to PIP among four distinct PIP criteria selected based on differing frequency and crude costs to validate the use of such characteristics for priority-setting. The crude healthcare costs, as well as the cost of the drug causing the PIP and the frequency of the PIP were identified as likely key characteristics of high-impact PIP.

Combined, these studies provide evidence on the overall burden of PIP, while also identifying likely characteristics of high-impact PIP. They suggest interventions at the health system level may be needed to address medication appropriateness and provide information which may be helpful to decision-makers when identifying which PIPs should be targeted for intervention, given no health system level interventions for PIP are currently in place.

Chapter 1: Introduction

1.1 Potentially Inappropriate Prescribing

Potentially Inappropriate Prescribing (PIP), also sometimes referred to as Potentially Inappropriate Medications (PIM), refers to the use of medications in older adults where the potential risks outweigh the potential benefits. There are a number of situations in which a prescribed medication may be inappropriate, including: 1) no clear evidence-based indication exists for the prescribed medication; 2) when a medication is prescribed longer, or in higher doses, than necessary; 3) medications prescribed in combination with medications from the same class; 4) in combination with other drugs that may cause drug-drug interactions, or situations where drug-illness interaction may occur; 5) when medications are prescribed in patients susceptible to a particular ADE (e.g. benzodiazepines in patients with history of falls); 6) when a medication is prescribed instead of a more cost-effective alternative that is equally, if not more, therapeutically effective [1]. PIP also includes situations where a drug should be prescribed, given evidence of benefit, but it is not. Situations such as these can also be called Potentially Inappropriate Omissions (PIO), and may occur due to a variety of reasons, including concerns over the potential for adverse events and the cost of the medication, or in some cases, a lack of prescriber knowledge [2–4].

Moving forward, PIP will be the collective term used to refer to both potentially inappropriate prescriptions and omissions in this thesis, unless otherwise specified.

1.2 Burden of medications in older adults

The impact of PIP is hypothesized to affect a substantial proportion of the elderly population in Ontario and Canada. PIP is most common in the elderly and its likelihood increases as patients

are prescribed more drugs than may be clinically necessary. For example, adults aged 65 years or older currently represent 15% of the Canadian population, but comprise 60% of all public drug program spending, consuming a disproportionate share of the prescribed medications in Canada according to a report by the Canadian Institute for Health Information [5]. Along with this high consumption of medications, polypharmacy, the use of five or more medications, or more medications than clinically necessary [6], is common in the elderly in Canada, with 65.9% of older adults having claims for 5 or more medications, and 27.2% of older adults having claims for 10 or more medications [7]. Polypharmacy is associated with significant downstream consequences, including Adverse Drug Events (ADEs), drug-drug interactions and drug-disease interactions [8].

ADEs are common in the elderly due to physiological vulnerability associated with aging and disease [9]. These contribute significantly to Emergency Department (ED) visits, unplanned hospitalizations [10], and in-hospital morbidity and mortality [11]. Many of these ADEs are due to potentially inappropriate prescriptions (PIP) and their consequences and costs would likely be avoided if inappropriate prescriptions were to be identified and prevented.

1.3 Identification of PIP clinically

A number of tools have been developed to identify PIP in clinical settings, including the STOPP/START criteria [12] (screening tool of older people's prescriptions (STOPP) and screening tool to alert to right treatment (START)) and the Beers criteria [13–17]. The STOPP/START criteria consist of a list of 81 STOPP (i.e. PIP) and 34 START (i.e. PIO) criteria organized by physiological organ system. The criteria were developed in Ireland by a multidisciplinary team of healthcare professionals, including geriatricians, pharmacists,

pharmacologists, and primary care physicians, though they tend to be more international in scope and application. Now in their second iteration, the STOPP/START criteria have been shown to be associated with ADEs and hospitalizations, and these criteria have been identified as the most promising to identify PIP in clinical settings [18].

The Beers criteria, developed in the United States, have been updated 4 times since 1991 with the most recent version published in 2015. Original versions focused on the American nursing home context, though the 2015 version has evolved to a total of 50 criteria, and was updated to address some of its short-comings to include drug-drug interactions and drug-disease interactions [17]. Unlike the STOPP/START criteria, the Beers criteria were not shown to be associated with ADE, discharge to higher level of care or in-hospital mortality [19], though a recent literature search has not identified any such studies using the 2015 Beers criteria, with only the 2012 Beers criteria as the most recent edition applied. Despite these apparent limitations, small subsets of the Beers criteria are being used in Canada as a healthcare system performance indicator [20].

When applied clinically, these tools are time-consuming and costly to apply to individual patients and, as a result, are under used. For example, in a recent project undertaken by Dr. Lise Bjerre's research team at the University of Ottawa, it took a clinical pharmacist over one hour per patient to complete an assessment for PIP, despite using a streamlined data collection tool [21]. Applying these clinical criteria to assess the appropriateness of prescribing to population-wide health administrative data can provide a unique opportunity to assess both the frequency of PIP and its associated costs, in terms of medication and health services use, at both the individual and population-level.

1.4 Identifying PIP in health administrative databases and its association with negative outcomes

The PIP-STOPP study is a CIHR-funded project with the aim of using subsets of the STOPP/START and Beers' criteria applicable to health administrative data housed at the Institute for Clinical Evaluative Sciences (ICES) to identify: 1) PIP at the population-level in Ontario; 2) its association with hospitalizations, ED visits and mortality; 3) its health system costs [22]. The first two objectives of this study have already been addressed through prior work. The first objective of the project was to translate the STOPP/START and Beers criteria into programming language that enabled their use with large, population-level routinely collected databases. Through this study, the prevalence of each individual PIP codable in health administrative databases (HAD), and PIP overall, was identified [23]. Through the second objective of this project, assessing the association between PIP and negative outcomes, it was determined that PIP are in fact strongly associated with adverse patient outcomes (ED visits, hospitalizations, death) at the population-level. Through both of these study objectives, the STOPP/START criteria were found to be more sensitive to the identification of PIP, as well as more strongly associated with patient outcomes, indicating they should be the criteria of choice in studies leveraging the use of HAD to identify PIP and evaluate its impact moving forward [24].

1.5 Knowledge gaps – health system costs of PIP in Canada and targets for intervention

The third component of the PIP STOPP project which has yet to be completed, and primary objective of this thesis, is to determine the impact of PIP on health system costs. PIP is associated with increased costs and health services use according to studies conducted in Ireland and the UK [25–27], but its economic impact in Canada has not been extensively characterized

[28]. A study by Morgan et al., applied a subset of the 2012 Beers criteria to the National Prescription Drug Utilization Information System to identify the medication costs associated with PIP across Canada [29]. This study determined that PIP medication costs were extensive, though this study used the Beers criteria and did not examine additional health system costs, such as those due to ED visits or hospitalization, nor were they able to adjust for potential confounders beyond age and sex, which is a limitation shared by several other international studies in this area.

This thesis project has the following two aims:

1. To assess the direct health system costs associated with PIP overall in Ontario from hospitalizations, ED visits and medications;
2. To validate the use of PIP frequency and crude healthcare system costs as indicators of high-impact PIP via estimation of the incremental costs associated with distinct PIP criteria.

Identifying the overall costs associated with PIP would provide further evidence to support PIP as a high priority for decision-makers by quantifying its overall burden and by providing a rationale for addressing PIP at the health system level. Given the difficulty with implementing macro, health system level interventions, validating the use of characteristics of PIP criteria, such as their frequency or crude healthcare system costs, by assessing the costs of specific PIP scenarios which vary by these characteristics would provide decision-makers with actionable information on which PIP to target. Such characteristics would help with the identification and prioritization of higher cost burden PIPs to intervene on at the micro, individual level. This would be particularly useful given how resource intensive conducting a study on a single PIP criterion is in terms of time and cost, let alone conducting such a study for dozens of criteria.

1.6 Note on thesis organization

This thesis is organized by manuscript, with three of the following four chapters comprising one manuscript each. The first manuscript is a protocol of the methodology used for the studies addressing objectives 1 and 2, providing rationale and details on the decisions made regarding the methods used. Chapter 3 corresponds to the results manuscript for objective one, assessing the overall cost burden of PIP. Chapter 4 illustrates the incremental costs associated with specific PIP scenarios and is intended to provide guidance on identifying costly PIPs based on their frequency and potential downstream costs. Finally, Chapter 5 provides an overall discussion and conclusion of the entire thesis project.

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Chapter 2: The health system costs of potentially inappropriate prescribing in Ontario, Canada: a protocol for a population-based cohort study

The following is a published manuscript formatted for submission to BMJ Open:
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2.1 Abstract

Introduction

Adverse drug events (ADEs) are common in older persons and contribute significantly to emergency department visits, hospitalisations and mortality. ADEs are often due to potentially inappropriate prescriptions (PIP) or potentially inappropriate omissions (PIO), and are avoidable if inappropriate prescriptions or omissions are identified and prevented. Identifying PIP/PIO at the population level through the application of PIP/PIO assessment tools to health administrative data can provide a unique opportunity to assess the economic burden of PIP/PIO on the healthcare system beyond medication costs which is yet to be done. The objective of this study is to assess the economic burden associated with PIP/PIO and to estimate the incremental costs associated with distinct PIP/PIO in the province of Ontario.

Methods and analysis

We will conduct a retrospective cohort study using Ontario's health administrative databases. Eligible patients aged 66 years and older who were prescribed at least one medication between 1 April 2003 and 31 March 2014 (approximately 2.4 million patients) will be included. Population attributable fraction methodology will be used to assess the overall burden of PIP in Ontario, while regression analyses will be used to estimate the incremental costs of having specific PIP criteria and aid in prioritising targets for intervention.

Ethics and dissemination

This study was approved by the Institutional Review Board at Sunnybrook Health Sciences Centre, Toronto, Canada. Dissemination will occur via publication, presentation at national and international conferences, and knowledge exchange with various stakeholders.

2.2 Introduction

Background

Adverse drug events (ADEs) are common in older persons due to physiological vulnerability associated with ageing and disease.[1] These contribute significantly to emergency department (ED) visits, unplanned hospitalisations,[2] and in-hospital morbidity and mortality.[3] Many of these ADEs are due to potentially inappropriate prescriptions (PIPs) or potentially inappropriate omissions (PIOs) (alternatively named potential prescribing omissions) and are avoidable if inappropriate prescriptions and/or omissions are identified and prevented. PIP/PIO is also most common in older persons and the likelihood of PIP increases as patients are prescribed more drugs than may be clinically necessary, which is defined as polypharmacy.[4]

A number of tools have been developed to identify PIP/PIO (referred to as PIP from now on unless otherwise specified) in clinical settings, including the STOPP/START criteria [5] (Screening Tool of Older Persons' Prescriptions/Screening Tool to Alert doctors to Right Treatment) and the Beers criteria.[6–10] These tools are time consuming and costly to apply individually and are underused. Applying these tools to assess the appropriateness of prescribing to population-wide health administrative data can provide a unique opportunity to assess both the frequency of PIP and its associated costs, in terms of medication and health services use, at both the individual and population level.

Evidence gaps to be filled

PIP is associated with increased costs and health services use according to studies conducted in Ireland and the UK,[11–13] but its economic impact in Canada is unknown. The PIP-STOPP study is a CIHR-funded project with the aim of using subsets of the STOPP/START and Beers' criteria applicable to health administrative data housed at the Institute for Clinical Evaluative

Sciences (ICES) to identify PIP and PIO at the population level in Ontario, its association with hospitalisations, ED visits and mortality, and health system costs.[14]

Identifying the overall health system costs associated with PIP would provide further evidence to support PIP as a high priority for decision-makers by quantifying its overall health system burden, while characterising the costs of specific PIP scenarios would provide these decision-makers with actionable targets to address PIP through a better understanding of the flow of costs attributable to different PIP scenarios and the identification of higher cost-burden PIPs.

This study protocol details the methods to assess the health system costs associated with PIP overall in Ontario, as well as to estimate the incremental costs of PIP scenarios which vary by their downstream healthcare resource use and by frequency. To address these knowledge gaps, the objectives of this study are to:

1. Assess the overall health system costs associated with PIP in Ontario.

2. Estimate the incremental costs associated with distinct PIP scenarios occurring in Ontario.

2.3 Methods

Methods regarding the study design, participants, datasets, exposure and cohort size for this study have been extensively described previously in the published protocol of its parent study [14] and are only summarised here. The methods common to both objectives, including study design, participants and data sources, are listed first, followed by the exposure, outcomes, covariates and statistical analyses relevant to each objective.

Study design

A population-based, retrospective cohort study design will be used, identical to that from previous publications from a larger retrospective, population-based cohort study on the identification of PIP and predicting patient outcomes in Ontario.[14]

Definition of observation periods

The study period will span from 1 April 2002 to 31 March 2015, which is based on the availability of the necessary databases. The patient accrual period will be from 1 April 2003 to 31 December 2014, allowing for a 1-year lookback period for prior health services utilisation and baseline covariates, as well as a 90-day follow-up period after the last possible PIP to allow time for identification of associated outcomes, **Figure 1**. We have chosen a 90-day observation window following instances of PIP in which to identify outcomes because we do not assume that the potential influence of PIP would extend beyond this period.

Participants

From the data housed at ICES, a large cohort of patients who are eligible for the study (approximately 2 million participants) has been identified. These patients are Ontario residents aged 66 years and older with Ontario Health Insurance Plan (OHIP) drug coverage (approximately 97% of Ontario seniors) who have been dispensed at least one prescription between 1 April 2003 and 31 December 2014.

Data sources

The proposed project will use population-level health administrative data from Ontario, which is housed at ICES.[15, 16] Accessing data through ICES allows for the linking of demographic, socioeconomic, hospital and outpatient health services, physician billing datasets, and prescription dispensation to Ontarians aged 65 years or older, or those requiring social

assistance.[17] Cost data are available for all physician claims, hospitalisations, ambulatory care services, home care services, long-term and complex continuing care, and medical devices in Ontario, while prescription medication cost data are available for those 65 years of age or older and those requiring social assistance. The following datasets will be linked to gather the appropriate and available exposure, outcome and covariate data necessary for analyses: Ontario Drug Benefits Claims Database (ODBD), Discharge Abstract Database, Same Day Surgery Database, National Ambulatory Care Reporting System, OHIP database, Registered Persons Database (see online supplementary appendix A for brief description of each). Additionally, five ICES-derived cohorts will be used for case ascertainment for specific STOPP/START criteria requiring the following diagnoses: asthma, diabetes, hypertension, chronic obstructive pulmonary disease and congestive heart failure.[18]

Objective 1: overall health system costs due to PIP

Exposure

The subset of STOPP/START criteria applicable to health administrative databases were identified based on the availability of the data necessary for their use and coded into a format applicable to ICES-housed health administrative data using a combination of medication, diagnostic (i.e., International Classification of Diseases Codes), healthcare services utilisation and physician billing codes. This process identified 64% of STOPP criteria and 27% of START criteria as applicable to health administrative data available through ICES. A manuscript describing the coding process in detail is in preparation.[19] The exposure of interest will be the first occurrence of any PIP identified using health administrative databases for each patient in the cohort during the study accrual period from 1 April 2003 to 31 December 2014. Unexposed patients will be those who have not experienced any PIP during the study accrual period.

Outcome

The primary outcome will be the combined medication, hospitalisation and ED visit costs attributable to PIP paid by the Ontario Ministry of Health and Long-Term Care over the 3 months following a PIP. These costs, from documented clinical events attributable to PIP, will be identified via population attributable fraction (PAF) methods.[20, 21] To identify costs, the ICES costing algorithm will be used.[22] This algorithm allows for the identification of costs from any health services covered by the OHIP over a defined time period.[22] All costs will be inflated to 2015 $C using Statistic Canada's Consumer Price Index.[23] The PAF estimates for hospitalisations, ED visits and medications will be derived via the incidence rate ratios (IRRs) obtained from Poisson or negative binomial regression models for each outcome, described in further detail in the statistical analyses section. Each PAF estimate will then be multiplied by the total cost of their respective healthcare service over the 90-day observation period for the whole population, which will be totalled to obtain the total costs attributable to PIP over the study period. Though we realise not all hospitalisations and ED visits will be causally related with PIP, ADEs are frequently under-recognised during ED visits and hospitalisation.[24, 25] As such, we chose to use reliably documented clinical events (hospitalisation and ED visits) and their costs, along with medication costs, as most suitable for the primary outcome. These costs were selected as they are the costs associated with the most reliably documented clinical events and those most likely to be linked to PIP. For medication costs, only those attributable to STOPP criteria will be determined and patients with PIP who either have a START criterion as their first PIP, or multiple first PIPs, will be excluded from this analysis. This is to ensure that all drug costs are attributable to the prescribing of a medication (i.e. STOPP criteria) and not to the omission of medication (i.e., START criteria), which would in fact result in a reduction in costs.

Covariates

Analyses will be adjusted for potential confounders which are available through provincial health administrative databases and either known or perceived to be associated with PIP or with our outcomes of interest (i.e., hospitalisation, ED visits and medication use), including age,[26, 27] sex,[27] income quintile,[27, 28] rurality, aggregated diagnosis group score (i.e., comorbidity status),[27, 29, 30] number of unique drug identification numbers (i.e., pills prescribed concurrently) in year prior to PIP,[31–35] number of prescribers in year prior to PIP,[36] whether the patient had a MedsCheck (billable medication review performed by a pharmacist, usually in the community) in year prior to PIP, number of days spent in hospital in year prior to PIP, ED visit in 6 months prior to PIP.[26, 27, 29, 37–41]

For this objective, the ascertainment of covariate status will be done at the PIP date for participants experiencing a PIP and at the randomly assigned index date for participants who do not experience a PIP, as further described below.

Statistical analyses

The direct costs associated with the occurrence of any first PIP in Ontario will be estimated by combing medication- related and non-medication-related costs attributable to PIP via the steps below.

Assignment of time to PIP for unexposed patients

To estimate the health system costs due to PIP, it is necessary to compare the number of days spent in hospital, the number of ED visits and the volume of newly prescribed medications in participants with and without PIP. To do this, we will need to assign an index date to participants without PIP so that they have comparable lookback and observation windows for covariate and

outcome ascertainment, respectively. The index date for participants not experiencing a PIP will be treated as missing at random. We will conduct parametric survival analysis on the participants within the cohort who have experienced a PIP, with their time-to-first PIP from cohort entry as the response variable in the model. The models will be stratified by sex and median age during cohort participation according to the following categories: 66–70, 71–75, 76–80, 81–85, 86–90, over 90. The models will be fitted to identify the appropriate distribution for its random error component. Once the best-fitting model has been identified, the resulting distribution and appropriate shape and scale parameters, depending on the distribution identified, will be applied to the participants without a PIP via the random number function in SAS [42] in order to randomly assign them a PIP index date and identify the start of their 90-day observation window. This random assignment will be done three times, with the first randomly assigned PIP index used for the primary analyses and most other subgroup and sensitivity analyses, while the other two will be used to conduct a sensitivity analysis to determine whether the random assignment method used impacts study results. Participants with an assigned PIP index date that falls beyond the end of their follow-up period will be excluded from all analyses. For both exposed and unexposed participants, we will determine whether they have at least 90 days between their PIP index date and the end of their follow-up. If this difference is less than 90 days, participants will be removed from the analysis.

This approach to assignment of an index date in non-PIP participants was selected over simple random assignment of time to PIP since the underlying distribution of time-to-first PIP in participants experiencing PIP is unknown and is not believed to be normally distributed and is also thought to vary by age and sex. We do not consider matching as an option due to the high prevalence if PIP in the older population resulting in a difficulty to find suitable matches for all

participants with a PIP. Additionally, the first day of a participant's inclusion in the study population for participants without PIP cannot be used as their PIP index date as this would make the unexposed group systematically younger than those exposed to PIP during analyses, resulting in confounding that may not be completely adjusted for even though age is being included in analyses as a covariate.

Medication use, ED visits and hospitalisations attributable to PIP

The IRRs for ED visits, days spent in hospital and medications for participants with PIP versus those without PIP will be determined via parameter estimates for the PIP variable from regression models for count data. Three models will be created, each with the response variable of either count of ED visits, days spent in hospital and total number of unique, newly prescribed medications in the 90-day period following their PIP date for participants with PIP, or the randomly assigned PIP index date for participants not experiencing a PIP. Each of the models will be adjusted for the covariates listed previously. For each outcome, either a Poisson or negative binomial model will be fitted based on a comparison of the mean of the response variable with its variance to determine if overdispersion is present.[43] Should the mean and variance be equal, or approximately so, then the Poisson model will be used. If the variance is greater and proportional to the mean, indicating overdispersion, then the negative binomial model will be used. The IRRs obtained via the parameter estimate for the PIP variable in the best-fitting model for each outcome will be used to derive their respective PAF in combination with the proportion of the population exposed to PIP (P_{exp}), obtained directly from our cohort as the PIP prevalence in the whole study population, via Levin's formula: $((P_{exp}*(RR-1))/((P_{exp}(RR-1))+1))*100$.[20,21]

Total costs attributable to PIP

The respective PAFs for ED visits, days spent in hospital and medications will be multiplied by the total costs for each of these health services, respectively, to obtain the total cost of each service use attributable to PIP over the 90-day observation period. These costs will then be combined to obtain the total health system costs attributable to PIP over the study period. The same methods will be used to obtain costs attributable to PIP by year.

Subgroup analyses

Similar methods to those listed above will be conducted in order to obtain the costs attributable to PIP by age, categorised by the median age of cohort participation based on the categories described above, and sex. Additionally, a subgroup analysis for the ED visit and hospitalisation costs will be conducted based on whether a patient's first PIP was a STOPP or START criteria, with patients experiencing multiple first PIPs excluded.

Objective 2: incremental costs of specific PIP criteria

Exposure

PIP will be identified using the same methods described in objective 1. Specific PIP criteria will be selected for the assessment of the incremental costs associated with each of them. For each of the criteria studied, the exposure of interest will be the first time the PIP of interest occurred for each participant in the cohort. Exposed participants must have never experienced another PIP prior to the PIP date, as well as during the 90-day observation window.

Unexposed participants will not have experienced any PIP during their cohort participation.

To identify the PIPs to model, each of the individual PIPs applicable to health administrative data was plotted on a graph according to their frequency (y-axis) by their crude average healthcare services costs (i.e., medication, hospitalisation and ED visits combined (x-axis), **Figure 2**. Two STOPP criteria falling on the high-cost plane were identified due to their potential for being high-impact PIPs, along with a high-frequency START criterion which also fell near this plane. A low-frequency/low-cost STOPP criteria was chosen to be used for comparison. The PIPs identified were: START A6, STOPP J6, STOPP K2, STOPP D8. START A6 is defined as the omission of ACE inhibitor with systolic heart failure and/or documented coronary artery disease. STOPP K2 is defined as the use of any neuroleptic drug. STOPP D8 is flagged as a PIP when anticholinergics and or antimuscarinics are prescribed in participants with delirium or dementia, due to risk of exacerbation of cognitive impairment. The final selected PIP, STOPP J6, is defined as the prescribing of androgens (male sex hormones) in the absence of primary or secondary hypogonadism. The full definitions as they appear in the STOPP/START criteria for each of the selected criteria are described in **Table 1** along with their categorised frequency and crude costs.[5]

Outcome

The outcome will be the combined hospitalisation, ED visit and PIP medication costs in the 90-day period following the PIP date. The ED visit and hospitalisation costs will be obtained via the ICES costing algorithm [22] and inflated to 2015 $C. Like the hospitalisation and ED visit costs, we will attempt to obtain the PIP medication cost via the ICES costing algorithm, though it may not be possible to obtain only the medication cost for the PIP medication, as the macro currently obtains all medication costs over a designated period as opposed to the costs of each individual medication. Should we be unable to obtain PIP medication costs via the macro, we will identify

the lowest hypothetical medication costs for each PIP via the prescribe smart mobile application,[44] which provides the drug unit price of all available drugs within Ontario and allows for easy comparison within class, at WHO Defined Daily Dose for each drug.[45] The drug cost of a daily dose will be multiplied by 90 to obtain the most conservative estimate of a 90-day supply to match the observation window. The highest and median prices for each PIP will also be obtained and used in sensitivity analyses, should this approach be used, to observe the PIP costing method's impact on incremental costs.

Covariates

The covariates of interest for objective 2 will be the same as in objective 1. Where they differ is in the assignment of the PIP date for ascertainment of covariate status in participants not experiencing a PIP. In objective 2, a subset of participants not experiencing a PIP will be selected for inclusion into the analysis based on having an exact, or similar, index date as a participant with a PIP. Once included, participants without a PIP will be assigned the same PIP date as the person with whom they share the exact or similar index date. This approach to participant inclusion and PIP date assignment has been selected since an efficient approach for participant selection and PIP date assignment that would be least likely to bias study results is necessary. The number of participants with the PIPs of interest ranges from several thousand to over 200 000, thus the number of unexposed participant's needs to be reduced in size for each of the analyses, precluding the inclusion of all unexposed participants in the cohort. Additionally, the index date is the least likely of all available covariates at time of participant selection to be associated with PIP or cost and outcomes, thus reducing the potential of introducing bias in participant selection.

Statistical analyses

The incremental costs associated with having each of the individual PIP criterion described in **Table 1** versus not having the PIP in question will be modelled using regression analyses. Due to the typical distribution associated with cost data, multiple candidate models will be assessed to identify the model that best fits the data. This process will begin with the fitting of an ordinary least squares regression and assessment of model fit, as well as a check for heteroscedasticity. If there is evidence of heteroscedasticity, we will then proceed with the selection of a generalised linear model. The link function and variance structure to be used will be determined using the TRANSREG function in SAS and modified Park's test, respectively. Should the Poisson variance structure be selected, the mean of the costs will be compared with the variance to determine whether overdispersion is present and whether a negative binomial model is preferred. All candidate models will be adjusted for the covariates described above. Each model's performance will be assessed using the Bayesian information criterion and graphical check of the distribution fit comparing the distribution of the predicted values with the expected values.

Patient and public involvement

The research questions addressed by this protocol were informed by the values and preferences of patients with regards to reducing their medication burden and improving their health outcomes, though no patients or public were directly involved in the development of this protocol. Results of this study will be disseminated to patient groups within our research networks.

2.4 Ethics and dissemination

Safety and confidentiality considerations

This study makes use of previously collected health administrative databases housed at ICES, accessed from ICES uOttawa, and does not require any additional intervention or data collection at the patient level. ICES links deidentified population-based health information at the population level in a way that ensures privacy and confidentiality to participants. As per ICES procedures, cell sizes of less than five will not be reported to address concerns about possible breaches of confidentiality.

Dissemination

Dissemination will primarily occur via publication of study results and presentation at national and international conferences. Professional networks will be used to promote dissemination with various stakeholders, including health policy-makers at the provincial and national levels.

Statement of originality

The assessment of the economic burden of PIP and PIO at the population level using linked health administrative databases is the first of its kind in any jurisdiction to the best of our knowledge. This is the first study of its kind leveraging linked health administrative databases to assess the health services costs of PIP and PIO beyond the medication costs alone, as well as the first study that will be able to adjust for potential confounders beyond age and sex.

Anticipated limitations

Our study is subject to limitations that are common to studies relying on health administrative databases which may affect our estimates of the prevalence of PIP and associated costs. It cannot be confirmed that participants adhered to the instructions regarding the medications dispensed to them, or regularly took them. Adherence to medication can only be assessed by comparing the date when an original prescription was scheduled to expire with the dispensation date of the

renewal prescription. It is also difficult to determine whether some of the PIP identified by the STOPP/START criteria are indeed inappropriate without clinical or diagnostic data that are unavailable to us.[46] Some of the STOPP/START criteria include over-the-counter medications or medications that are not covered by Ontario's public medication plan (ODB), and thus are not captured in the ODBD or identified as a PIP in our database. Additionally, we are unable to determine the cost of PIP medications from the linked health administrative databases due to the complexity and time required to identify specific prescriptions from a total of over half a billion prescriptions. As such, a conservative approach will be used to identify medication costs as described in the outcomes section. Despite these limitations, we are confident our study will produce useful, conservative estimates of the health system costs associated with PIP.

2.5 References for Chapter 2

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2.6 Tables and figures for Chapter 2

Table 1. Definitions for PIP criteria to be modelled as part of the second objective, along with their frequency and cost classification

PIP	Definition	PIP Frequency	Costs
START A6	Angiotensin Converting Enzyme (ACE) inhibitor with systolic heart failure and/or documented coronary artery disease	High	Mid
STOPP K2	Neuroleptic drugs	Mid	Mid
STOPP D8	Anticholinergics/antimuscarinics in patients with delirium or dementia (risk of exacerbation of cognitive impairment)	Low	High
STOPP J6	Androgens (male sex hormones) in the absence of primary or secondary hypogonadism (risk of androgen toxicity; no proven benefit outside of the hypogonadism indication).	Low	Low

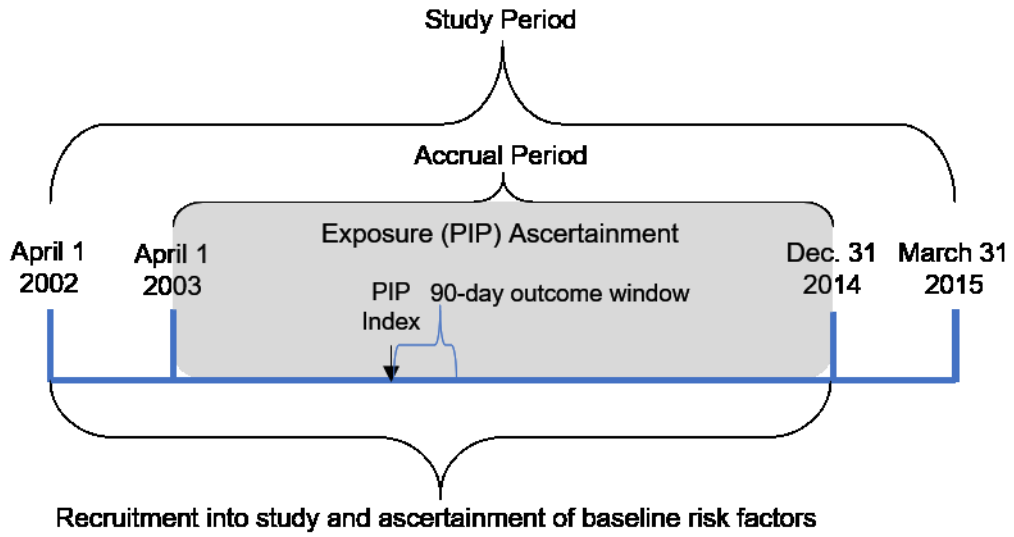

Figure 1. Definition of observation period

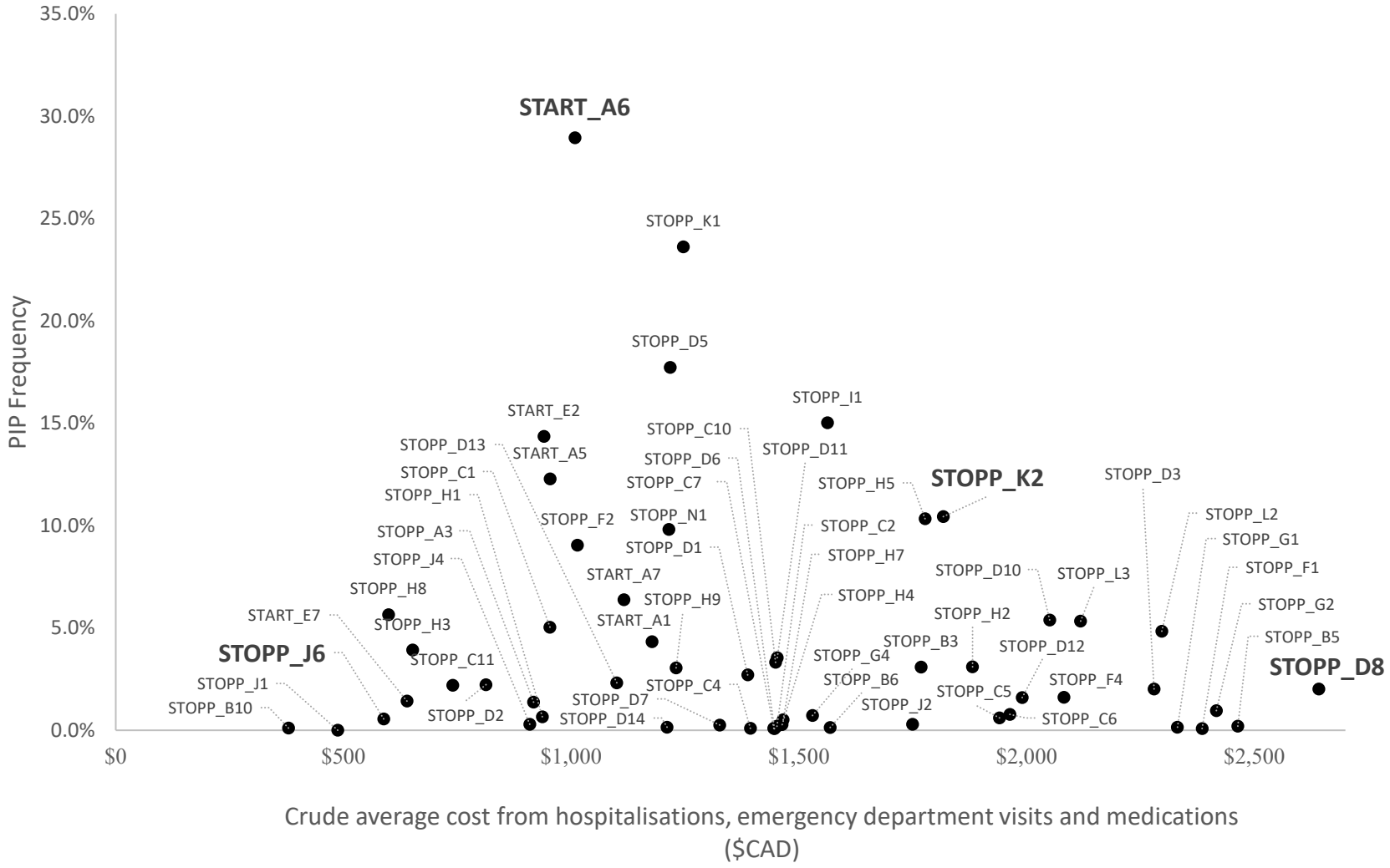

Figure 2. Assessment of PIP frequency by crude costs (from hospitalisations, emergency department visits and medications) to determine PIP scenarios to be modelled

2.7 Appendix for Chapter 2

A. Brief description of data sources

Adapted with permission from:

Bjerre LM, Ramsay T, Cahir C et al. Assessing potentially inappropriate prescribing (PIP) and predicting patient outcomes in Ontario's older population: a population-based cohort study applying subsets of the STOPP/START and Beers' criteria in large health administrative databases. BMJ Open. 2015;5(e010156).

Ontario Drug Benefits Claims Database (ODBD). The Ontario Drug Benefit program provides drug benefits for all Ontario residents aged 65 and older and those with disability/social assistance benefits. The ODBD contains a number of data related to prescription drugs, including drug identification number (DIN), quantity of drugs provided, number of days supplied (which can be used to compute the daily dose), itemized cost, dispensing fee, long-term care indicators, the plan affiliated with the prescription (e.g. Seniors, Trillium, Ontario Works etc.), the date the drug was dispensed, and patient and prescriber identifiers (encrypted). Additionally, ICES maintains a list linking DINs to their associated drug and product names, subclass information, pharmacologic-therapeutic classification group (PCG) codes, drug strength, route of administration, and first and last dispensing dates from the ODB.[1]

Discharge Abstract Database (DAD). The DAD captures all acute care hospitalizations in Ontario dating back to 1988. Each row in the DAD records demographic, diagnostic, procedural, and treatment information for a given hospitalization.[1]

Same Day Surgery Database (SDS). The SDS contains patient-level data for day surgery institutions in Ontario. Every record corresponds to one same-day surgery or procedure stay.[1]

National Ambulatory Care Reporting System (NACRS). The NACRS captures all visits to hospital EDs beginning in 2002. As with the DAD, each row of the NACRS contains demographic, diagnostic, procedural, and treatment information for each emergency room visit [35].[1]

Ontario Health Insurance Plan (OHIP) database. The OHIP database captures health services billing claims paid by the Ontario Health Insurance Plan to providers. Each row in the OHIP database records the patient, provider, and diagnosis/procedure being claimed for remuneration.[1]

Birth date and death date of every individual eligible for Ontario health service will be obtained from the *Registered Persons Database (RPDB*).[1]

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Chapter 3: The health system costs of potentially inappropriate prescribing: a population-based, retrospective cohort study using linked health administrative databases in Ontario, Canada

3.1 Link to previous manuscript

The previous chapter described in detail the methods used for the individual studies undertaken in Chapters 3 and 4. The study design, population, exposure and outcomes of interest, as well as the statistical analyses were clearly outlined. One of the priorities of this chapter was to present the rationale for specific methodological decisions that had to be made, with a focus on their impact on study validity versus alternative options. Overall, Chapter 2 presented the steps necessary to answer the primary research objectives of this thesis, namely: 1. To assess the direct health system costs associated with PIP overall in Ontario from hospitalizations, ED visits and newly prescribed medications; 2. To estimate the incremental health system costs associated with select PIP criteria.

In Chapter 3, the results of the first of the two research objectives, namely the overall health system costs associated with PIP in Ontario, are reported. As discussed previously, PIP is an important issue in Canada and abroad, and while we are aware of its impact on drug expenditures and its association with negative health outcomes such as ED visits, hospitalizations and mortality, we have little information on its absolute impact on health system related expenditures beyond drug costs. Identifying such costs may provide further evidence to decision makers that PIP is a significant issue, as well as provide evidence to help prioritize PIP and associated medication appropriateness as a health-system wide issue among other high priority healthcare system issues.

In Chapter 3, I present a manuscript addressing the aim of assessing the overall health system costs from any PIP in Ontario. I first describe the rationale behind the conduct of this study,

followed by a methodology section that summarizes the methods presented in Chapter 2. Next, I present the results from this study, including the burden of PIP in the overall population and per person, as well as the burden of PIP broken down by age and sex. Finally, I present a discussion of the results, including their interpretation, as well as their implications for future research.

3.2 Manuscript

The following is an unpublished manuscript formatted for submission to Drugs and Aging (not yet submitted, planned submission date: December 2018)

Authors: Cody D. Black, Kednapa Thavorn, Doug Coyle, Lise M. Bjerre

3.2.1 Abstract

Objective
The aim of this study was to determine the health system costs from hospitalizations, emergency department (ED) visits and medications due to potentially inappropriate prescribing (PIP) in Ontario, Canada at the population-level.

Methods
A retrospective cohort of individuals ≥66 years of age and prescribed at least one medication from April 1st, 2002 to March 31st, 2015 was identified using linked population-level health administrative databases from Ontario, Canada. Patients were identified as having a PIP or no PIP by applying a subset of the STOPP/START criteria. The number of days spent in hospital, new medications prescribed and ED visits in the 90-days following a PIP or patient index date were captured, as well as the total costs from each of these health services. Poisson and negative binomial count regression models were used to generate incidence rate ratios for each outcome given the presence of PIP versus no PIP and combined with the prevalence of PIP to generate population attributable fractions (PAF). The PAF was then multiplied by the cost for each health service to obtain the costs attributable to PIP in the whole cohort, and by age and sex.

Results
PIP was associated with an increased rate of hospitalization (Incidence Rate Ratio (IRR): 2.77, 95% CI: 2.72 to 2.82), ED visits (IRR: 1.87, 95%CI:1.82-1.92), and newly prescribed medications (IRR: 1.13, 95%CI:1.13-1.14), resulting in PAFs of 55.7%, 37.9%, and 5.0% for each outcome, respectively. PIP was responsible for 38.8% of the total spent on these healthcare services ($1,221,309,870), or $772 per PIP per person. Costs attributable to PIP decreased with age despite increasing prevalence.

Conclusions
PIP in older adults is a significant source of health system costs from healthcare service use beyond medications costs, with a significant portion of hospitalizations and ED visit costs attributable to PIP. Future work should focus on identifying strategies and priorities for intervention, including a focus on addressing PIP in younger seniors.

3.2.2 Introduction

Rationale

Potentially inappropriate prescribing (PIP) describes the occurrence of prescribing practices that may increase a patient's risk for adverse health outcomes given safer, more effective treatment options are available for a particular indication, or simply where the risks of therapy outweigh the benefits [1]. As a result, medication appropriateness in older persons is an important priority due to the potential for adverse drug events, increased morbidity, unplanned hospitalizations [2], ED visits [3] and mortality. In order to avoid negative outcomes such as these from PIP, criteria, including the STOPP/START (screening tool of older persons' potentially inappropriate prescribing /screening tool to alert doctors to right treatment) [4] and Beers criteria[5], have been developed to help clinicians identify PIP in clinical settings and improve medication appropriateness.

Recently, subsets of both the STOPP/START and Beers criteria codable in large health administrative databases have been applied to such data in Ontario housed at the Institute for Clinical Evaluative Sciences (ICES) [6]. Through this initiative, the prevalence of PIP and its association with ED visits, hospitalization and mortality was identified. Instances of PIP were found to be frequent and associated with all three of these outcomes [7]. Still, little is known about the health system costs associated with PIP at the population-level.

Previous studies have identified significant medication costs associated with PIP [8–10], while others have assessed the health system costs of specific PIP criterion [11], but none to our knowledge have assessed the health system costs from ED visits and hospitalization due to PIP overall at the population-level. Contextualizing the health system cost burden of PIP, in conjunction with what we know about their association with health outcomes, may help inform

policy discussions around the improvement of prescribing quality and medication appropriateness. They may also provide further evidence to various stakeholders to support the implementation of interventions at the health system level to support the broad improvement of medication appropriateness.

Objective

The aim of this study was to determine the health system costs from hospitalizations, ED visits, and newly prescribed medications due to PIP in Ontario, Canada at the population-level. We also aimed to assess whether these costs differed between men and women, or between age groups.

3.2.3 Methods

The methods for this study and their rationale have been described extensively elsewhere in a study protocol [12]. As such, the methods are summarized below. The RECORD statement checklist of items is presented in **Table A, Appendix 1**. This study was approved by the institutional review board at Sunnybrook Health Sciences Centre, Toronto, Canada.

Study Design

A population-based, retrospective cohort study design was used, spanning from April 1st, 2002 to March 31st, 2015. The patient accrual period was from April 1st, 2003 to December 31st, 2014, allowing for a one-year lookback period for prior health services utilization and baseline covariates, as well as a 90-day follow-up period after the last possible PIP to allow time for identification of outcomes.

Data sources

This study leveraged population-level health administrative datasets from Ontario housed at the Institute for Clinical Evaluative Sciences (ICES) [13,14]. These datasets allowed for the linking of demographic, socioeconomic, hospital and outpatient health services, physician billing datasets, and prescription dispensation to all Ontarians aged 65 years or older with Ontario Health Insurance Plan (OHIP) coverage [15]. The following datasets were linked to gather desired exposure, outcome and covariate data necessary for analyses: Ontario Drug Benefits Claims Database (ODBD), Discharge Abstract Database (DAD), Same Day Surgery Database (SDS), National Ambulatory Care Reporting System (NACRS), OHIP database, Registered Persons Database (RPDB) [16].

Participants

All Ontario residents aged 66 years of age or older with valid Ontario Drug Benefit coverage (approximately 97% of Ontario seniors) and dispensed at least one prescription during the accrual period were eligible for the study.

Exposure

The exposure of interest was the first occurrence of any PIP (yes/no) identified using health administrative data. Participants could experience multiple first PIPs from different criterion on the same day, though this only had bearing on the medication outcome models and certain sensitivity analyses which are further described below. PIP were identified via the application of a subset of STOPP/START criteria applicable to health administrative databases [6]. This subset of criteria was coded into a format applicable to ICES-housed health administrative data using a combination of medication, diagnostic (i.e. International Classification of Diseases), healthcare services utilization and physician billing codes. The coding process is described in detail elsewhere [6].

Assignment of time-to-PIP for unexposed patients

To compare the outcomes of interest in participants with and without PIP, the index date in participants without PIP was treated as missing at random. We randomly assigned an index date to participants without a PIP so that they would have comparable lookback and observation windows for covariate and outcome ascertainment, respectively.

Parametric survival analysis using a variety of distributions was conducted on the participants who experienced a PIP to characterize their time-to-PIP, defined as the time from their accrual into the cohort until the time of the occurrence of their first PIP. Models were stratified by sex and median-age during cohort participation according to the following categories: 66-70, 71-75, 76-80, 81-85, 86-90, over 90. The distribution, shape and scale parameters from the best fitting models were then used with the random number function in SAS [17] in order to randomly assign a time-to-PIP to participants without a PIP based on their age and sex. This was then converted to an index date by adding the time-to-PIP to the participant's accrual date. Participants assigned an index date that fell beyond the end of their follow-up period were excluded from analyses, while all participants, with or without a PIP, who had an observation window smaller than 90 days were excluded from all analyses. The distribution of time-to-index date between participants with and without PIP was assessed following the imputation process using a visual check of distributions, as well as a comparison of the mean time-to-index date between exposed and unexposed groups.

Outcome

The primary outcome of interest was the combined medication, hospitalization and ED visit costs (reasons for the selection of these costs available in the study protocol [12]) attributable to PIP paid by the Ontario Ministry of Health and Long-Term Care, both in total, as well as per

individual (an outcome not included in the study protocol) of all the costs for these outcomes over the 90-day period following the first PIP occurrence for participants with PIP, or index date for unexposed participants. To identify these costs, the ICES costing algorithm was used [18] and all costs were inflated to 2017 Canadian dollars using the Statistic Canada's Consumer Price Index [19]. For participants not experiencing a PIP, the 90-day follow-up period began on the date of random index date assignment, described in further detail above.

Covariates

All analyses were adjusted for potential confounders either known or perceived to be associated with PIP or with our outcomes of interest (i.e. hospitalization, ED visits and medication use) and available within our linked health administrative datasets, including age [20,21], sex [21], income quintile [21,22], rurality, aggregated diagnosis group (ADG) score (i.e. comorbidity status) [21,23,24], number of unique drug identification numbers (i.e. pills prescribed concurrently) in year prior to PIP [25–29], number of prescribers in year prior to PIP [30], whether the patient had a MedsCheck (billable medication review performed by a pharmacist, usually in the community) in year prior to PIP, number of days spent in hospital in year prior to PIP, and ED visit in 6 months prior to PIP [20,21,23,31–35]. Definitions for these variables have been previously described elsewhere [36]. Covariate ascertainment was done at the date of a participant's first PIP and at the randomly assigned index date for participants who did not experience a PIP.

Statistical analyses

<u>Medication use, ED visits and hospitalizations attributable to PIP</u>

Once outcome and baseline covariate information were gathered for all participants, three models were created, one for each outcome: count of ED visits, days spent in hospital and total

number of unique, newly prescribed medications. Prior to fitting each model we tested for overdispersion to determine whether a Poisson or negative binomial distribution was most appropriate for our count regression models [37]. The IRR obtained via the parameter estimate for the PIP variable in the model for each outcome was used in conjunction with the population prevalence of a first PIP ever to derive the population attributable fraction (PAF) via Levin's formula: $((P_{exp}*(RR-1))/((P_{exp}(RR-1))+1))*100$ [38,39]. This formula divides the product of the population prevalence multiplied by the IRR minus one, by the sum of one plus the product of the population prevalence multiplied by the IRR minus one. This figure is then multiplied by 100 to obtain a percentage. For the medication outcome model, only patients with a PIP due to a STOPP criterion and no overlapping, or multiple first, PIPs were included to ensure only a potential error of commission was responsible, as we were unable to determine what the exact first PIP was in such cases.

Total costs attributable to PIP

PAFs for ED visits, days spent in hospital and newly prescribed medications were then multiplied by the total costs for each of these health services, respectively, to obtain the cost of each health service use attributable to PIP over the 90-day observation period after a PIP or randomly assigned index date. These costs were also combined to obtain the total health system costs attributable to PIP.

Subgroup and sensitivity analyses

The methods listed above were used to obtain the costs attributable to PIP by age, categorized as described above, and sex. Sensitivity analyses were also conducted, including the assignment of two additional random index dates to persons without PIP to determine whether the random assignment method potentially biased study results, as well as the removal of people with their

first PIP occurring on their date of entry into the cohort to assess for the presence of incidence-prevalence bias due to the potential that these were prevalent and not incident PIPs. Additionally, the removal of people with multiple first PIPs and overlapping PIP during their observation period, two of the conditions applied to the inclusion of participants in the newly prescribed medications models, was applied to the hospitalization and ED visit outcome models to assess the impact of the first PIP alone on those outcomes. Finally, an analysis stratified by type of first PIP (i.e. STOPP (PIP) or START (PIO)) was also conducted to determine the impact of PIP type on hospitalization and ED visits.

3.2.4 Results

Baseline characteristics

A total of 2,477,122 residents of Ontario prescribed at least one medication between April 1st, 2003 and Dec 31st, 2014 were identified. After assigning a random index date to persons without a PIP, the cohort was further restricted to 2,256,153 total study participants with at least 90 days of follow-up time for outcome ascertainment, see **Figure A, Appendix 2** for a description of how the final study cohort was obtained. Among included participants, time-to-index date was well balanced between participants with and without PIP after random index date assignment.

Among the identified cohort, the mean age was 72.1 (SD=7.4) and 44.8% were male (1,010,761/2,256,163), **Table 2**. When comparing baseline characteristics between the two groups, patients with PIP were, on average, older, had more comorbidity (identified via ADG), concurrent medications, days spent in hospital and prescribers, as well as were more likely to have a previous ED visit and to be in the lowest income quintile. No missing outcome data and very little missing covariate data were identified, with all of it pertaining to either place of

residence or income quintile. Data for these variables were missing in less than 0.4% of participants.

PIP prevalence by age and sex

After assessment of baseline characteristics, we further assessed PIP prevalence and prevalence of a first PIP due to a STOPP criterion only, in the whole cohort, as well as by age and sex. While 70.1% (1,581,897/2,256,163) of cohort members had at least 1 PIP, only 40.2% (907,993/2,256,163) of cohort members had a first PIP due to a STOPP criterion, **Table 3**. The overall prevalence of PIP remained similar between males and females, though females had a higher proportion of first PIPs due to a single STOPP criterion, indicating males had a higher prevalence of a first PIP due to a START criterion or multiple first PIPs. With regards to age, overall PIP prevalence tended to increase with age, from 57.0% (592,532/929,009) in the 66-70-year-old age group to 84.2% (215,660/256,025) in the 81-85 year-old age group, and then remaining consistent thereafter, while the number of first PIPs due to a STOPP criterion tended to decrease with age.

Costs attributable to PIP in whole cohort

The total costs from hospitalizations, ED visits and newly prescribed medications from April 1st, 2003 to December 31st, 2014 in the 90-days after index date were $2,000,286,464, $172,289,790 and $975,197,362 for each outcome, respectively, and PIP was associated with increased rates for all three outcomes, **Table 4**. Participants with PIP had a 2.77 (95% CI: 2.72 to 2.82) times higher rate of hospitalization than those without PIP, leading to a PAF of 55.3% (95% CI: 54.7%-56.1%). Increased rates of ED visits and newly prescribed medications were also observed in participants with PIP versus those without, with 1.87 (95%CI: 1.82-1.92) and 1.13 (95%CI: 1.13-1.14) times higher rates, respectively. When combined with the PIP prevalence,

PAFs of 37.9% (95%CI: 36.5%-39.2%) for ED visits and 5.0% (95%CI: 5.0%-5.3%) for newly prescribed medications were observed.

After multiplying the costs for hospitalization, ED visits and newly prescribed medications in the 90-day follow-up period by their respective PAFs, a total of $1,221,309,870 out of $3,147,773,616 (38.8%) from all three health services were attributable to PIP, with the highest proportion of costs stemming from hospitalizations and fewest from new medications. The total cost from all three healthcare services per individual with a PIP was $772.83 (95%CI: $761.36-$784.19).

Costs attributable to PIP by age and sex

When assessing the costs attributable to PIP between males and females, few differences were observed, though PIP was still associated with higher rates of outcomes in both subgroups, **Table 5**. Males with PIP tended to have higher rates of each outcome than females with PIP when compared to participants without a PIP of their respective sex, and the observed difference in total costs attributable to PIP and cost per person with a PIP is likely due to the higher PAF of PIP for hospitalization costs in males.

Assessment of the costs attributable to PIP by age category displays a trend for prevalence and PAF. While prevalence of PIP tends to increase with age, the PAF tends to decrease with age due to a general trend of decreasing rates of outcomes due to PIP by age category. For example, while the youngest age category (66 to 70) had a 57% PIP prevalence (40.6% STOPP only) versus 81.2% (36.7% STOPP only) for the oldest age category (90+), the PAFs for hospitalization, ED visits and newly prescribed medications were 55.2%, 33.7% and 3.5% respectively for the youngest age group, versus 34.2%, 28.5% and 2.9%, respectively, for the

oldest age group. Additionally, due to the larger population size of the youngest age group, the absolute costs to the healthcare system from the outcomes of interest due to PIP are much larger ($350,800,451) compared to the oldest age group ($27,213,543).

Sensitivity analyses

The random index date assignment had a limited impact on study results, as the IRR estimates remained stable when the second and third random index date assignments were assessed, and they were within 10% of the primary analysis IRRs, **Table A, Appendix 3.** Comparable results were also observed when assessing the removal of participants whose first PIP occurred on their first day of accrual into the study cohort to ensure no incidence-prevalence bias was present in our analyses. Changes in the IRRs for hospitalizations, from 2.77 (95% CI: 2.72-2.82) to 2.03 (95%CI: 1.98 to 2.08), and ED visits, form 1.87 (95%CI: 1.82-1.92) to 1.58 (95% CI: 1.57-1.60), were observed after the removal of participants with multiple first PIPs and overlapping PIPs within their outcome observation period. When comparing the IRRs when restricting the cohort to participants with a STOPP criterion as their first PIP versus those with a START as their first PIP, higher rates of hospitalizations and ED visits were observed in the participants with a STOPP criterion, and given their higher prevalence, their costs would be as well.

3.2.5 Discussion

The results presented within this article describe the burden of PIP, further enhancing our understanding of this prevalent issue beyond the tabulation of medication costs, using a large cohort of older persons in Ontario identified using linked health administrative databases. We have found that older persons with a PIP experience higher rates of hospitalization, ED visits, and newly prescribed medications than their counterparts who have also been prescribed a

medication but have not experienced a PIP. When combined with the high prevalence of PIP in the population, PIP was responsible for a significant portion of healthcare expenditures related to these outcomes.

Beyond the identification of PIP as a high cost issue, this study has important findings with policy implications. Much of the discussion around medication appropriateness and PIP centers on the cost of the offending drugs themselves, but what we found is that the medication costs likely have a lower impact on healthcare expenditures than hospitalizations and ED visits. Not only would reducing PIP decrease drug expenditures, it could also prevent significant morbidity that leads to even larger downstream expenditures via lengthy hospital stays and unnecessary ED visits. While this research was conducted using a cohort of residents of Ontario, due to the large cohort size spanning a diverse region of Canada, these results are likely to be generalizable to other provinces in Canada and countries with similar healthcare systems and populations. The proportion of expenditures due to PIP identified in this study provide further evidence for PIP as a high priority target for intervention at the population-level in Canada and in other jurisdictions where PIP is prevalent. This study provides evidence on the total burden of PIP that could help decision-makers with priority setting when PIP is compared to other important healthcare issues. Additionally, this study highlights the need for macro, health-system level interventions to address PIP given its large burden and the fact that this burden is from a broad range of criteria in different disease areas and drug classes that might otherwise need to be addressed with micro-level, individual interventions. The PAF and costs related to PIP would decrease should the prevalence of PIP decrease based on these interventions.

The subgroup and sensitivity analyses provide further characterization of the burden of PIP and may provide some direction on priorities for intervention. When assessing the health system

costs due to PIP by age, while PIP prevalence increased by age, the cost impact of PIP decreased with age due to decreasing IRRs which indicate costs in the older populations are likely explained by other factors, such as comorbidity. Combined with their larger population size, this resulted in larger absolute costs in the younger age group, providing evidence for PIP interventions to be prioritized in younger seniors, as interventions targeting this population might have a greater impact. Additionally, the sensitivity analysis assessing the impact of the first PIP ever with no other concurrent or overlapping PIPs displays the importance of intervening as soon as possible on a PIP. The primary analysis results show the average impact of all PIPs on outcomes, while the first PIP only results show how vital it may be to intervene on the first PIP.

To the best of our knowledge, this is the first study of its kind to assess the burden of PIP beyond just medication costs at the population-level using linked health administrative data. Our findings of increased medication expenditures due to PIP are in line with previous research, though these studies only assessed the costs of a medication responsible for a PIP and no costs related to newly prescribed medications that may have resulted from a PIP, i.e. a prescribing cascade [8–10]. One of these studies assessed the cost of PIP in Canada using a subset of the Beers list, which previous research has shown to be not as sensitive at identifying PIP than the STOPP/START criteria [6], while the other two studies were conducted in European settings [8,9].

Our study is subject to certain limitations around the methodology and data used. We used the PAF, which has several key assumptions: that the effect of PIP is reversible, interventions exist to address it and that the relationship between PIP and the outcomes assessed is causal [40]. The assumption with the greatest impact on the interpretation and validity of our results it that of causality, as observational studies such as ours typically only identify associations between an

exposure and outcome of interest at best. While the relationship between PIP and the outcomes of interest addresses a number of the traditional Hill's criteria for assessing causal relationships [41], we cannot say for certain that PIP causes hospitalization, ED visits and additional prescription of medications. One other limitation related to this is the issue of residual confounding. Since our data source was not initially intended for research, we were limited by the availability of variables for the control of confounding within our models. While we are confident that the covariates used addressed much of the confounding by indication, it is possible that there is still some leftover confounding by unmeasured variables. It should also be noted that the use of the STOPP/START criteria in HAD compared to clinical data in Ontario is currently being validated. While there is the potential for low sensitivity and specificity to detect PIP in HAD from these codes, the process used to identify PIP criteria applicable to HAD was conservative and transparent [36]. Additionally, since we are using health administrative data, and not clinical data, and a conservative approach to identifying PIP was used, some PIPs cannot be identified and we are thus likely to be underestimating the prevalence of PIP [6]. Given prevalence is an important factor in the PAF, this indicates that we may be underestimating the impact of PIP. One important strength of this study to note is the method use to assign a random index date to participants without a PIP. An unbiased approach to identifying a 90-day observation period for outcome ascertainment was needed, and the use of the distribution of time-to-PIP from accrual into the study cohort from patients with PIP and applying it to patients without a PIP afforded us with the best solution. This may be useful in future drug safety and effectiveness studies facing a similar situation.

3.2.6 Conclusion

PIP in older adults is not only common and costly with regards to medication expenditures, it is also a significant source of costs from downstream events like hospitalizations and ED visits. Future work should focus on identifying strategies and priorities for intervention at both the health system and individual levels. Younger seniors are at the highest risk of hospitalization and ED visit from PIP and have the highest cost burden, indicating that they may be a subgroup of interest when identifying populations where intervention may be most effective. Additional work should be conducted to identify priority PIPs that are most highly associated with negative burden and costs given a lack of current health system level interventions to address all PIP. Intervening on PIP would not only lead to savings on prescription drugs costs but would also provide a health benefit to patients while significantly reducing downstream health system costs.

3.2.7 References for Chapter 3

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3.2.8 Tables and figures for Chapter 3

Table 2. Characteristics of study population

CHARACTERISTIC	Had PIP (N=1,581,897)	No PIP (N=674,266)	Primary analysis cohort (N=2,256,163)
Mean age (SD)	74.0 (7.6)	69.8 (5.8)	72.1 (7.4)
Sex (Male)	44.6%	45.5%	44.8%
Number of ADGs (SD)	9.2 (3.7)	6.3 (3.4)	8.3 (3.7)
Number of concurrent meds (SD)	5.0 (3.1)	2.1 (2.1)	4.2 (3.1)
Mean number of days spent in hospital in year prior to index or assigned index date (SD)	3.6 (11.6)	0.6 (4.8)	2.7 (10.1)
≥1 ED visits in 6 months prior to index or assigned index date	32.0%	10.3%	25.5%
Income quintile			
1 - lowest	20.1%	16.4%	19.0%
2	20.9%	19.6%	20.5%
3	19.5%	19.8%	19.6%
4	19.4%	20.9%	19.9%
5 - highest	19.6%	23.0%	20.6%
Missing	0.4%	0.4%	0.4%
Place of residence (urban)[a]	85.1%	85.2%	85.1%
Number of prescribers in the year prior to first PIP (SD)	2.7 (2.1)	1.9 (1.4)	2.5 (1.9)
MedsCheck in year prior	7.6%	7.5%	7.6%

ADG – aggregate diagnosis group; ED – emergency department; PIP – potentially inappropriate prescription; SD – standard deviation;

[a]0.11% of cohort had missing information on place of residence

Table 3. Prevalence of PIP among whole cohort and by subgroups

Group	Number of persons with a PIP (STOPP criterion as first PIP)	Number of persons eligible for study cohort	Prevalence (STOPP criteria only)
Whole cohort (STOPP criteria only)	1,581,897 (907,993)	2,256,163	70.1% (40.2%)
Sex			
Female	876,808 (546,190)	1,244,562	70.5% (43.9%)
Male	705,089 (361,803)	1,011,601	69.7% (35.8%)
Median Age During Cohort Participation			
66-70	529,532 (377,006)	929,009	57.0% (40.6%)
71-75	393,177 (218,908)	529,320	74.3% (41.4%)
76-80	283,494 (138,957)	350,753	80.8% (39.6%)
81-85	215,660 (100,369)	256,025	84.2% (39.2%)
86-90	112,228 (51,125)	132,145	84.1% (38.7%)
>90	47,806 (21,628)	58,911	81.2% (36.7%)

PIP – potentially inappropriate prescription; STOPP – screening tool of older people's prescriptions

Table 4. Primary analysis – costs attributable to PIP

Health Service/Cost Category	Number of participants with PIP	Incidence rate ratio with PIP vs no PIP (95% CI)	PIP Prevalence	Population Attributable Fraction (%; 95%CI)	Total costs (2017 CAD$)	Costs attributable to PIP (2017 CAD$)[b]	Cost per individual (2017 CAD$; 95%CI)
Hospitalization	1,581,897	2.77 (2.72-2.82)	70.1%	55.3 (54.7-56.1)	2,000,286,464	1,107,608,294	699.97 (691.01-708.66)
ED visits	1,581,897	1.87 (1.82-1.92)	70.1%	37.9 (36.5-39.2)	172,289,790	65,268,856	41.24 (39.74-42.69)
Medication[a]	907,993	1.13 (1.13-1.14)	40.2%	5.0 (5.0-5.3)	975,197,362	48,432,720	53.32 (53.32-57.21)
				Total	3,147,773,616	1,221,309,870	772.83 (761.36-784.19)

95%CI – 95% confidence interval; CAD$ - Canadian dollars; PIP – potentially inappropriate prescription

[a]Includes only those with a STOPP criterion as their first PIP. All participants with a START criterion as their first PIP, multiple first PIP, or an overlapping second PIP within their 90-day outcome observation window were removed and the prevalence was recalculated.

[b]Costs attributable to PIP were determined by multiplying unrounded PARs by the total costs.

Table 5. Costs attributable to PIP by sex and median age during cohort participation

Health Service/Cost Category	Number of participants with PIP	Incidence rate ratio with PIP vs no PIP (95% CI)	PIP Prevalence	Population Attributable Fraction (%; 95%CI)	Total costs (2017 CAD$)	Costs attributable to PIP[b]	Cost per PIP per individual (2017 CAD$; 95%CI)
Sex							
Female							
Hospitalization	876,808	2.74 (2.67-2.82)	70.5%	55.1 (54.1-56.2)	981,015,469	540,446,255	616.20 (604.81-628.610
ED visits	876,808	1.76 (1.73-1.79)	70.5%	38.0 (36.6-39.3)	91,389,084	34,743,543	39.61 (38.17-40.99)
Medication[a]	546,190	1.12 (1.12-1.13)	43.9%	5.0 (5.0-5.4)	529,162,647	26,481,255	48.47 (48.47-52.29)
				Total	1,601,567,201	601,671,053	686.01 (673.18-702.18)
Male							
Hospitalization	705,089	2.81 (2.74-2.89)	69.7%	55.8 (54.8-56.8)	1,019,270,993	568,579,220	806.16 (792.07-821.54)
ED visits	705,089	1.84 (1.81-1.87)	69.7%	36.9 (36.1-37.7)	80,900,705	26,272,393	42.36 (41.39-43.30)
Medication[a]	361,803	1.15 (1.14-1.15)	35.8%	5.1 (4.8-5.1)	446,034,717	22,731,389	62.81 (58.82-62.81)
				Total	1,546,206,415	621,185,312	880.75 (863.64-897.06)
Age							
66-70							
Hospitalization	529,532	3.16 (3.06-3.26)	57.0%	55.2 (55.1-54.0)	580,137,432	320,126,033	604.37 (591.50-616.60)
ED visits	529,532	1.89 (1.86-1.92)	57.0%	33.7 (32.9-34.4)	53,601,957	18,040,386	34.06 (33.29-34.81)
Medication[a]	377,006	1.09 (1.09-1.10)	40.6%	3.5 (3.5-3.9)	358,392,982	12,634,032	33.50 (33.50-37.08)
				Total	992,132,371	350,800,451	662.28 (648.64-677.81)
71-75							
Hospitalization	393,177	2.31 (2.21-2.40)	74.3%	49.3 (47.3-51.0)	445,287,220	219,634,531	558.45 (536.00-577.26)
ED visits	393,177	1.69	74.3%	33.9	35,881,151	12,160,742	30.92

		(1.63-1.74)		(31.9-35.4)			(29.09-32.36)
Medication[a]	218,908	1.22 (1.21-1.23)	41.4%	8.3 (8.0-8.7)	216,478,481	18,070,957	82.52 (79.08-85.95)
				Total	697,646,851	249,866,231	635.32 (609.12-657.48)
76-80							
Hospitalization	283,494	2.14 (2.04-2.25)	80.8%	47.9 (45.7-50.2)	411,617,375	190,998,074	695.96 (662.79-729.37)
ED visits	283,494	1.59 (1.53-1.65)	80.8%	32.2 (30.0-34.4)	32,393,464	10,457,373	36.87 (34.25-39.34)
Medication[a]	138,957	1.17 (1.16-1.18)	39.6%	6.3 (6.0-6.7)	169,187,105	10,671,285	76.77 (72.53-80.99)
				Total	613,197,944	211,445,822	770.47 (732.59-808.40)
81-85							
Hospitalization	215,660	1.83 (1.73-1.94)	84.2%	41.1 (38.1-44.2)	323,496,810	133,076,875	616.89 (570.86-662.53)
ED visits	215,660	1.61 (1.56-1.67)	84.2%	33.9 (32.0-36.1)	27,778,415	9,426,111	43.70 (41.26-46.44)
Medication[a]	100,369	1.13 (1.12-1.14)	39.2%	4.8 (4.5-5.2)	132,504,575	6,425,014	64.00 (59.29-68.66)
				Total	483,779,798	148,928,001	690.37 (639.72-740.92)
86-90							
Hospitalization	112,228	1.79 (1.66-1.93)	84.1%	39.9 (35.7-43.9)	168,275,404	67,172,054	598.35 (535.04-657.86)
ED visits	112,228	1.51 (1.46-1.59)	84.1%	30.0 (27.9-33.2)	15,797,747	4,741,944	42.24 (39.25-46.67)
Medication[a]	51,125	1.11 (1.10-1.12)	38.7%	4.1 (3.7-4.4)	69,661,327	2,844,397	55.62 (50.75-60.45)
				Total	253,734,477	74,758,395	665.94 (597.41-732.07)
>90							
Hospitalization	47,806	1.64 (1.48-1.82)	81.2%	34.2 (28.0-40.0)	71,472,223	24,441,122	511.11 (419.17-597.40)
ED visits	47,806	1.49	81.2%	28.5	6,837,056	1,946,038	40.70

		(1.41-1.58)		(25.0-32.0)			(35.71-45.78)
Medication[a]	21,628	1.08 (1.06-1.10)	36.7%	2.9 (2.2-4.9)	28,972,894	826,382	38.20 (28.85-65.45)
				Total	107,282,173	27,213,543	569.08 (467.93-672.79)

95%CI – 95% confidence interval; CAD$ - Canadian dollars; PIP – potentially inappropriate prescription

[a]Includes only those with a STOPP criterion as a their first PIP. All participants with a START criterion as their first PIP, multiple first PIP, or an overlapping second PIP within their 90-day outcome observation window were removed and the prevalence was recalculated.

[b]Costs attributable to PIP were determined by multiplying unrounded PARs by the total costs.

3.2.6 Appendix 1

Table A. The RECORD statement – checklist of items, extended from the STROBE statement

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	40	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	40 42 42
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	43		
Objectives	3	State specific objectives, including any prespecified	44		

		hypotheses			
Methods					
Study Design	4	Present key elements of study design early in the paper	44		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	44		
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants	45	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use	44-45 44-45 Study flow displays the number of

		(b) Cohort study - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case		of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	participants at each step. Decided against other graphical representation.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	45-46	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	45 – referenced the coding process which is described details elsewhere
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	44		
Bias	9	Describe any efforts to address potential sources of bias	44 - Described in study protocol		

Study size	10	Explain how the study size was arrived at	N/A – based on eligibility criteria solely		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	47 – referencing previous protocol		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of	47-49		

		sampling strategy (e) Describe any sensitivity analyses			
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	Previously reported in study protocol
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	Previously reported in study protocol
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed)	49, 75	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	49, 75

		(b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram			
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	49 49 NA		
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or	NA		

		summary measures			
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Unadjusted estimates not applicable Confounder adjusted estimates: 50		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	51-52		
Discussion					
Key results	18	Summarise key results with reference to study objectives	52-53		
Limitations	19	Discuss limitations of the study, taking into account	54-55	RECORD 19.1: Discuss the implications of using data that were not created	54-55

		sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	55-56		
Generalisability	21	Discuss the generalisability (external validity) of the study results	53		
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	5		
Accessibility of protocol, raw data, and programm		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data,	Access to raw data N/A given data source Protocol referenced

ing code				or programming code.	in methods section (pg. 44)

Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

3.2.7 Appendix 2

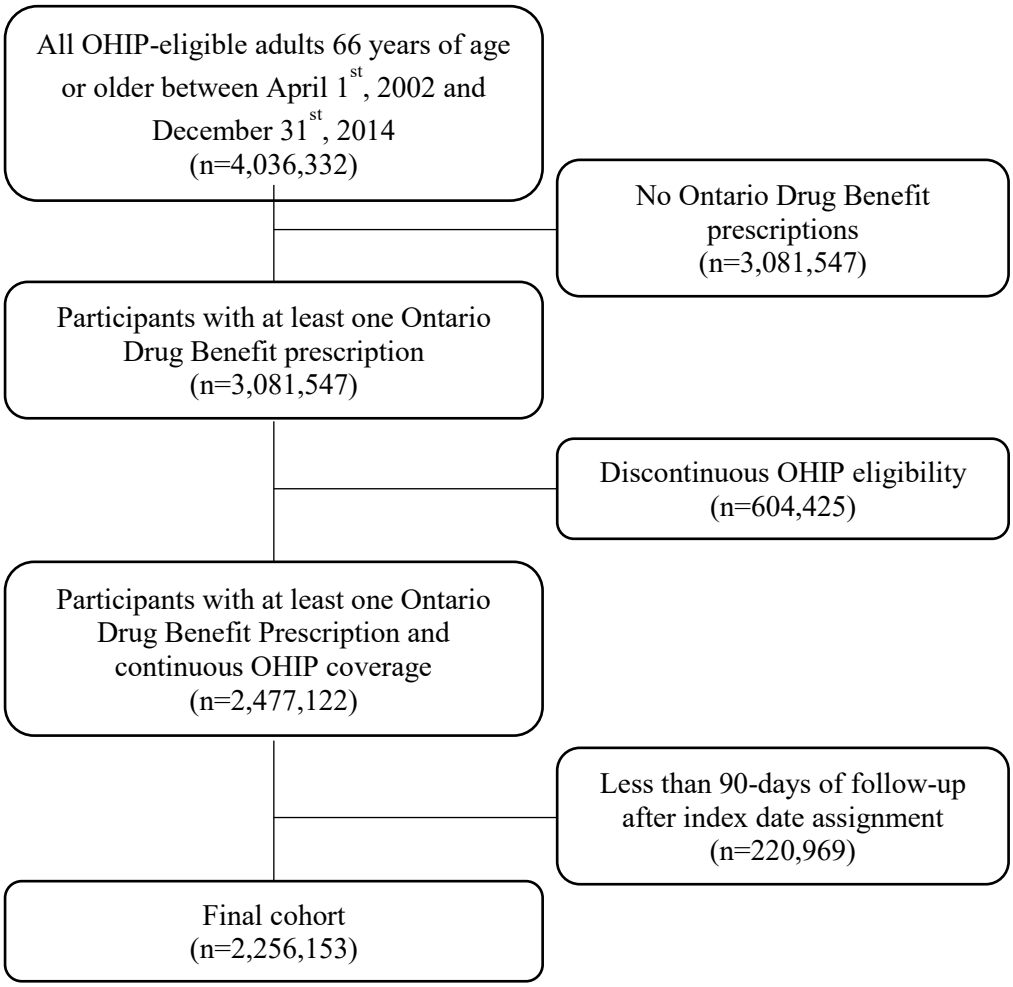

Figure A. Final cohort creation steps

3.2.8 Appendix 3

Table A. Comparison of primary analysis incidence rate ratios with those from sensitivity analyses.

Health Service/Cost Category	Primary analysis IRR (N=2,256,163; STOPP only, N=1,582,259)	Second Random Index Assignment (N=2,217,437; STOPP only, N=1,543,533)	Third Random Index Assignment (N=2,170,156; STOPP only, N=1,506,466)	Removal of participants with first pip on accrual date (N=2,141,517; STOPP only, N=1,483,724)	Removal of people with multiple first PIP and overlapping PIP in observation period[b] (N=1,651,175)	STOPP Criterion only[b] (N=1,543,533)	START Criterion only[b] (N=1,130,034)
Hospitalization	2.77 (2.72-2.82)	3.05 (2.99 to 3.11)	3.14 (3.08-3.21)	2.82 (2.77 to 2.88)	2.03 (1.98 to 2.08)	3.15 (3.08 to 3.22)	2.17 (2.11 to 2.24)
ED visits	1.87 (1.82-1.92)	1.98 (1.95 to 2.00)	1.97 (1.94-1.99)	1.88 (1.86 to 1.90)	1.58 (1.57 to 1.60)	2.26 (2.23 to 2.28)	1.35 (1.33 to 1.37)
Medication[a]	1.13 (1.13-1.14)	1.15 (1.15-1.15)	1.13 (1.13-1.14)	1.13 (1.13-1.14)	NA	NA	NA

IRR – incidence rate ratio; PIP – potentially inappropriate prescription; START – screening tool to alert to right treatment; STOPP – screening tool of older people's prescriptions

[a]Includes only those with a STOPP criterion as their first PIP. All participants with a START criterion as their first PIP, multiple first PIP, or an overlapping second PIP within their 90-day outcome observation window were removed and the prevalence was recalculated.

[b]Not applicable to medications, as these restrictions had already been placed for this outcome.

Chapter 4: Identifying characteristics of high-impact potentially inappropriate prescriptions: a comparison of incremental cost estimates for four STOPP/START criteria using health administrative databases in Ontario, Canada

4.1 Link to previous manuscript

The previous chapter addressed the first aim of this thesis project, which was to determine the overall health system costs from medications, ED visits and hospitalizations due to PIP at the population-level. Via a retrospective cohort of participants 66 years of age or older in Ontario identified using linked health administrative databases in Ontario, it was determined that a sizeable portion of the costs from hospitalizations, ED visits and newly prescribed medications were attributable to PIP. In all, $1,221,309,870 out of $3,147,773,616 were due to PIP, and on average, an instance of PIP cost $772 per person. The costs attributable to PIP decreased with age, despite the prevalence of PIP increasing with age, indicating younger seniors may be a subset of the population in whom interventions to address PIP would have the biggest impact to reduce negative health outcomes and their associated costs.

In the following chapter, I present the results of the second objective of this thesis project, which was to validate the use of PIP frequency and crude healthcare system costs as indicators of high-impact PIP via estimation of the incremental costs associated with distinct PIP criteria. While the previous chapter demonstrated just how significant the burden of PIP is, the reality is that not all PIPs are equal with regards to their impact. Some may be more impactful than others when it comes to their association with ED visits and hospitalizations, while the costs of the drugs involved can vary greatly between PIP. As such, estimating the incremental costs of PIP with different drug costs, healthcare utilization and frequency profiles, and validating their use, may provide guidance to decision makers when trying to determine priorities for intervention by identifying characteristics common among costly PIP. This information is especially important

should macro-level, health system wide approaches to addressing medication appropriateness and all PIP not be feasible. Such information to aid with prioritization of the highest impact PIP when not all PIP can be addressed could help ensure that the greatest impact is made when deciding which PIP(s) should be intervened on first.

In this chapter I present the manuscript of a study which assessed the incremental costs of four different case-study PIPs. The rationale for the study is described first, followed by a summary of the methods that have been previously presented in the study protocol from Chapter 2. The incremental costs of having each case-study PIP versus not having any PIP are then described, as well as the absolute costs of each PIP based on their prevalence. The results of the study are then followed by a discussion that includes an interpretation of the results, along with their implications on future directions and research related to medication appropriateness.

4.2 Manuscript

The following is an unpublished manuscript formatted for submission to Health Affairs (not yet submitted, planned submission date: December 2018)

Authors: Cody D. Black, Kednapa Thavorn, Doug Coyle, Lise M. Bjerre

4.2.1 Abstract

Given the prevalence of inappropriate prescribing, the aim of this study was to validate the use of potentially inappropriate prescribing (PIP) frequency and crude healthcare system costs as indicators of high-impact PIP via estimation of the incremental costs associated with distinct PIP criteria. We used linked health administrative databases in Ontario, Canada to assess the incremental health system costs from hospitalizations, emergency department visits and medications, after controlling for potential confounders, from April 2003 to March 2015 of four distinct potentially inappropriate prescribing criteria selected and classified by crude healthcare costs and their frequency of occurrence a priori. PIP were classified as having low, mid or high costs and frequency, respectively, and the four PIPs were each selected as a representative case of different cost and frequency classification groupings (e.g. low cost, low frequency). We found that the incremental costs of having the PIP being studied tended to be higher for the PIPs classified as having high ($238.51, 95% CI: $47.62-$429.40) to moderate ($68.66, 95%CI: $50.01-$87.31) crude costs than those classified as having low crude costs ($-9.10, 95%CI: -$147.02 to $128.82). Additionally, the prevalence had a greater impact on the total estimated costs to the healthcare system than the incremental cost itself. This study provides evidence for the use of crude costs and prevalence as characteristics of high impact potentially PIP to help with priority setting.

4.2.2 Introduction

Potentially inappropriate prescribing (PIP) describes the occurrence of prescribing practices that may increase a patient's risk for adverse health outcomes given safer, more effective treatment options are available for a particular indication, or simply where the risks of therapy outweigh the benefits [1]. PIP is common in older persons due to a higher prevalence of multimorbidity and polypharmacy, and can often lead to adverse drug events (ADE), such as unplanned hospitalizations [2], ED visits [3] and mortality [4], which place a significant clinical burden on patients and cost burden on the healthcare system.

A number of tools have been developed to identify PIP in clinical settings in older adults, including the STOPP/START criteria (Screening Tool of Older Persons' Potentially Inappropriate Prescribing /Screening Tool to Alert doctors to Right Treatment) [5]. A subset of the criteria from this tool has now been operationalized to identify PIP using linked, large health administrative databases in Ontario, Canada [6]. The application of this subset has been used to show that PIP are significantly associated with hospitalization, ED visits and mortality at the population-level [7]. In addition to their clinical impact, PIP have been shown to be a significant source of medication [8–10] and health system expenditures (Chapter 3).

While there is evidence available on the burden PIP has on PIP-specific medication costs to the healthcare system [9], as well as its overall burden on related health system expenditures (Chapter 3), there is not much information available on which specific criteria are most burdensome relative to others. Additionally, there is not much information available on whether there are characteristics of PIP that may help identify which PIP are most burdensome to the healthcare system. It is possible that some PIP criteria have higher up-front medication costs, yet lead to little downstream healthcare resource use, while other PIP may have low up-front

medication costs, yet lead to frequent and costly downstream resource use. Furthermore, the total health system costs from a specific PIP criterion are likely to be impacted by how prevalent the PIP is in the general population, which is another factor for consideration when prioritizing targets for intervention. Understanding and comparing the incremental and total costs to the health system for different PIPs with different profiles of frequency, crude resource use and medication costs may help identify potential characteristics of high-impact PIP to help with priority-setting for decision-makers and clinical practice guideline developers alike to use when determining which PIPs to target for intervention. Such characteristics could provide guidance on which PIPs to target to reap the greatest reduction in negative health outcomes and resulting health system costs without having to conduct further resource intensive projects to cost out each separate PIP criterion to adequately prioritize them, given how many PIP criteria exist.

To address this gap in knowledge, the aim of this study was to validate the use of PIP frequency and crude healthcare system costs as indicators of high-impact PIP via estimation of the incremental costs associated with distinct PIP criteria. This study allowed for the assessment of how the incremental and total health system costs associated with older persons experiencing PIPs, compared to older persons not experiencing a PIP, varied by PIPs with different classifications of prevalence and crude costs from medications, ED visits and hospitalization (i.e. low, mid, high). The PIPs selected for cost modelling were identified within the study protocol [11].

4.2.3 Methods

The methods are summarized below. A protocol describing the methods and their rationale in greater detail has been published elsewhere [11]. The RECORD statement checklist of items is

presented in Supplement A**.** This study was approved by the institutional review board at Sunnybrook Health Sciences Centre, Toronto, Canada.

Study Design, Data Sources and Participants

We used a population-based, retrospective cohort study design spanning from April 1st 2002 to March 31st 2015 using population-level health administrative data (HAD) from Ontario, Canada which is housed at the Institute for Clinical Evaluative Sciences (ICES) [12,13]. Accessing data through ICES allows for the linking of demographic, socioeconomic, hospital and outpatient health services, physician billing datasets, and prescription dispensation to Ontarians aged 65 years or older, or those requiring social assistance [14]. From the data housed at ICES, we identified a cohort of patients aged 66 years or older with Ontario Health Insurance Plan drug coverage dispensed at least one prescription medication between April 1, 2003, and December 31, 2014. This accrual period allowed for a one-year lookback period to identify confounding variables and to allow for at least 90 days of follow-up for outcomes.

Exposure

Previous work has been conducted on the application of the STOPP/START criteria for use in HAD [6]. For this study, we sought to identify individual criteria to evaluate as case studies. Identification of which PIPs to be used as case studies was based on assessment of a scatter plot of all PIP plotted by their frequency and crude costs from hospitalizations, ED visits and PIP causing medications, which was previously presented in the study protocol [11], Supplement B. Crude costs were obtained by multiplying the unadjusted ED visit and hospitalization event rate by the average cost for each respective event according to the Canadian Institutes for Health Information, and adding this to a 90-day supply of the cheapest medication that could be

responsible for the PIP. Based on the scatter plot, each PIP was classified as having low, mid or high frequency and crude costs, respectively, and four PIPs were selected based on having different representative crude cost and frequency classifications. The four PIPs identified as case studies were START A6, STOPP J6, STOPP K2 and STOPP D8 (See **Table 6** for full definitions and frequency and cost classifications), and are defined as follows: START A6, defined as the omission of an angiotensin converting enzyme (ACE) inhibitor with systolic heart failure and/or documented coronary artery disease; STOPP K2, the prescribing of any neuroleptic drug; STOPP D8, defined as anticholinergics/antimuscarinics in patients with delirium or dementia; STOPP J6, defined as androgens in the absence of primary and secondary hypogonadism. For each criterion studied, the exposure of interest was the first time the PIP of interest occurred for each participant in the cohort. Additionally, they must have never experienced another PIP at any point in the observation period.

Unexposed participant identification and eligibility

For each criterion, a subset of participants not experiencing a PIP over the entire study period was selected for inclusion into the analysis based on having a cohort entry date that approximated that of a participant with a PIP. Once included, participants without a PIP were assigned the same PIP index date as the person with whom they shared the approximate entry date. This was done to obtain a PIP index date for which to collect baseline covariate information and to denote the beginning of the 90-day outcome period for participants without PIP.

In the cases of START A6 and STOPP D8, unexposed participants had to have a diagnosis of systolic heart failure and/or documented coronary artery disease, and delirium or dementia, respectively, as these were the conditions necessary to have the respective PIP. In the case of

STOPP J6, only men were eligible to be included as unexposed participants given the medication causing the PIP of interest could only be prescribed in men.

Outcome

The outcome of interest was the combined hospitalization, ED visit and PIP medication costs in the 90-day period following the PIP index date. The ED visit and hospitalization costs were obtained via the ICES costing algorithm [15], inflated to 2017 Canadian dollars. PIP medication costs were identified as the lowest hypothetical 90-day supply of a drug causing the PIP, at the World Health Organization Defined Daily Dose, via the Prescribe Smart mobile application [16], which searches the Ontario Drug Benefit e-formulary and provides the drug unit prices of all available drugs and their dosages, and allows for easy comparisons within drug classes [17]. The highest and median prices for each PIP-related drug were also obtained for sensitivity analyses. For the START A6 criterion, the medication costs were added to the unexposed participants, as in this case the PIP is due to a medication omission and the unexposed patients are those receiving the drug of interest. The incremental costs for hospitalizations and ED visits were also assessed separately, as well as the estimated total health system costs from ED visits, hospitalizations and medication costs for the entire population experiencing a case-study PIP combined based on the incremental costs obtained (and 95% CI) multiplied by the prevalence of the PIP as a first PIP ever and at any time point during the study period (i.e. as a first, second, third PIP or beyond).

Covariates

We identified the status as of PIP index date of covariates that were either associated with PIP or the outcome of interest that could be confounding variables to be included in all statistical analyses. These variables are listed in Supplement C.

Statistical analyses

The incremental costs from hospitalizations and ED visits associated with having each of the individual PIP criterion described in **Table 6** versus not having the PIP in question were modelled using regression analyses. This is a deviation from the protocol, as we had initially intended to include drug costs in the regression outcome measure, but the inclusion of drug costs rendered models unstable and unable to converge and given how drug costs were estimated in this study (see Outcome section above) they were a constant and may not have sufficient variation to be explained by the model.

Due to the highly-skewed distribution associated with cost data, multiple candidate models were initially assessed based on a defined process listed in the protocol [11]. Given the proportion of zero costs for our outcome of interest (generally between 50 and 90%), a two-part approach was selected, with a logistic regression to measure the probability of having any costs, followed by a generalized linear model with a gamma distribution and log-link to model the predicted costs in participants with any costs. Predicted costs were obtained by multiplying the probability in the first part by the predicted costs in the second part. To assess model performance, the Root mean squared error and Bayesian information criterion were used to compare this model to other potential candidate models to confirm the two-part model with gamma distribution and log-link as the best fitting model.

The predicted costs were calculated using the recycled predictions approach to create an identical covariate structure and to avoid reintroducing confounding when calculating incremental costs [18–20]. This approach requires that a model be built with the cohort participants' original exposure status, followed by predicting the outcome twice using the original model's parameter estimates to obtain predicted values, once when the cohort's exposure status is set to 1 (having

PIP), and then again when exposure status is set to 0 (no PIP) for everyone. The primary outcome, incremental costs from PIP, was calculated by combining the predicted ED visit and hospitalizations costs with the medication costs and taking their mean and subtracting the mean costs of participants without PIP from the mean costs of participants with PIP.

4.2.4 Results

Over the study accrual period, the total number of persons experiencing each of the case-study PIPs at any point was 717,119 for START A6, 49,792 for STOPP D8, 13,754 for STOPP J6 and 258,617 for STOPP K2. When case-study participants were restricted to only those experiencing the PIP as their first PIP ever with no additional, overlapping PIP, and the unexposed participants were selected, samples sizes varied. The START A6 case-study cohort was the largest with nearly 216,054 people with this as their first PIP (12,474 eligible unexposed), versus 5,246 for STOPP J6 (4,958 unexposed), 3,421 STOPP K2 (3,127 unexposed), and 729 with STOPP D8 (513 eligible unexposed) (see Supplement D for figures A to D describing cohort creation for each PIP criterion).

When comparing the baseline characteristics of patients with PIP versus no PIP in each of the case-study cohorts, the only common trends that emerged were that participants with PIP in each cohort tended to have more comorbidity (identified via ADG), concurrent medications and unique prescribers, as well as a higher proportion of participants with an ED visit in the six months prior, Supplement E. Additionally, the mean number of days spent in hospital was greater in participants with PIP, except for the STOPP J6 cohort, where it was balanced between groups, while participants with PIP also tended to have a higher proportion of MedsCheck in the year prior, except in the START A6 cohort, where participants without a PIP had a higher

proportion receiving a MedsCheck in the year prior. Participants with PIP also tended to be in the lowest income quintiles, except for those in the STOPP J6 cohort. Age and place of residence tended to be well balanced between groups, except in the STOPP K2 cohort where patients with PIP were older on average and more likely to live in an urban setting.

In all case-studies, participants with PIP had higher unadjusted mean costs than participants without PIP. To assess the incremental costs due to each PIP case study, two-part models with a gamma distribution and log link were found to best fit the data, particularly due to the large mass of zero costs.

Two of the case study PIPs, STOPP D8 and STOPP K2, resulted in positive adjusted mean incremental costs when participants with the PIP were compared to those without PIP, **Table 7** (model outputs available in Supplement F, Tables A to L). Participants with STOPP D8 as their first PIP ever had adjusted mean costs of $1207.26 versus $968.75.20 for those without PIP, resulting in adjusted mean incremental costs of $238.51 (95%CI: $47.62 to $429.40), and the ratio of costs between participants with PIP and those without was 1.25. In the other case-study with positive incremental costs, participants with STOPP K2 as their first PIP ever had adjusted mean incremental costs of $68.66 (95% CI: $50.01 to $87.31), based on adjusted mean costs of $152.62 for participants with the PIP versus $83.9 for those without. Additionally, participants with STOPP K2 as their first PIP ever had 1.82 times higher costs than participants without a PIP.

Of the other two case-studies, START A6 and STOPP J6, participants with START A6 also had positive incremental costs compared to those without a PIP, while participants with STOPP J6 had negative incremental costs compared to those without a PIP, though their 95% confidence

intervals crossed zero, which indicates that these results are not statistically significant. Participants with START A6 as their first PIP ever had adjusted mean costs of $327.02 versus $299.01 for those without PIP for adjusted mean incremental costs of $28.00 (95% CI: -$133.86 to $189.87). The ratio of costs between participants with PIP and those without was 1.09. In the final case-study, STOPP J6, participants with this PIP as their first PIP ever had mean costs of $150.16 versus $159.26 for those without PIP. Their adjusted mean incremental costs were -$9.10 (95% CI: -$147.02 to $128.82) their cost ratio was 0.94.

When the total health system costs from ED visits, hospitalizations and medications for all participants experiencing each of the PIP medications combined were considered, total incremental costs were influenced by the prevalence of participants experiencing the PIP as their first ever, or when the entire population experiencing the PIP at any point during the study period was considered. As with the incremental cost results, total costs were positive for all case-study PIPs, save for the costs from STOPP J6, though when a range of potential total costs is considered using the 95% confidence intervals from the adjusted mean incremental costs results from above, the ranges for PIPs START A6 and STOPP J6 cross zero, **Table 8.**

The two PIPs with positive incremental costs, STOPP D8 and STOPP K2, had total cost ranges that were entirely positive. For STOPP D8, when the population experiencing this PIP as their first PIP ever was considered, the total costs were $173,876 (95%CI: $34,718 to $313,034). These costs rose considerably to $11,876,044 (95%CI: $2,371,297 to $21,380,792) when the entire number of persons experiencing this PIP at any point during the study period was considered. The STOPP K2 PIP had the highest total health system costs of all case-studies, with an estimated total cost of $234,883 (95%CI: $171,094 to $298,672) from participants experiencing this PIP as their first PIP ever. This estimate rose to $17,756,441 (95%CI:

$12,934,182 to $22,578,701) when including all persons experiencing this PIP at any point during the study period.

We next assessed the adjusted mean incremental costs due to each PIP case-study by source of expenditure, **Table 9**. For hospitalization costs, there was considerable uncertainty for three of the case-study PIPs, each of which had adjusted mean incremental cost confidence intervals crossing zero dollars, save for STOPP K2, where participants had an adjusted mean incremental cost of $25.74 from hospitalizations (95%CI: $9.58 to $41.90) when compared to participants without a PIP. There was less uncertainty around the incremental costs for ED visits, as all 95% confidence intervals were statistically significant. For two of the case-studies, START A6 and STOPP K2, the incremental costs were miniscule with increased costs of $2.70 (95%CI: $2.36 to $3.03) and $5.61 (95%CI: $4.33 to $6.89) for participants with the respective PIP when compared to participants without a PIP. The incremental costs from ED visits in the other two case studies were higher in magnitude, though they had different directions of effect. Participants with the STOPP J6 PIP had fewer ED visit costs (-$18.64; 95%CI: -$21.14 to -$16.14) compared to participants without a PIP. Participants with STOPP D8 as their first PIP ever had $18.84 in increased ED visit expenditures (95%CI: $12.33 to $25.35) compared to participants without a PIP.

The medication expenditures could vary greatly depending on the PIP, but in each case they appeared to be the only source of expenditure that was consistent with the direction of effect of the combined incremental costs. Additionally, the lowest medication costs estimated in each case were either the largest influence on incremental cost, or nearly equivalent with the next largest expenditure of influence.

4.2.5 Discussion

The aim of this study was to validate the use of PIP frequency and crude healthcare system costs as indicators of high-impact PIP via estimation and assessment of the incremental costs associated with distinct PIP criteria. The incremental health system costs associated with older persons experiencing PIP in Ontario, when compared to persons never experiencing a PIP, were assessed to determine how they varied by different case study PIPs with different crude healthcare costs and frequencies, as this would help to identify characteristics of high impact PIPs. Validating characteristics of high impact PIP, such as the crude costs or prevalence, would be helpful, as they would allow for an approach to prioritization of PIPs for intervention instead of conducting resource intensive incremental cost studies to identify the adjusted costs for the 60+ criteria applicable to HAD in Ontario.

When adjusted mean incremental costs were assessed, two of the case study PIPs, STOPP D8 and STOPP K2, resulted in increased adjusted mean incremental costs from medications, hospitalizations and ED visits combined. Participants with START A6 had increased costs from PIP and those with STOPP J6 as a first PIP ever had decreased costs from PIP, though there is uncertainty in these estimates given their 95% confidence intervals crossed zero. When looking at estimates of the potential total health system costs from each case-study PIP for everyone experiencing the PIP combined, comparable results for each PIP were observed, though the prevalence played a large role in determining the total costs due to PIP in the population, far outweighing the magnitude of the incremental costs. Additionally, breaking down the incremental costs by source of expenditure shows that each PIP is unique with regards to whether hospitalizations or ED visits have a larger impact, though medications may play a key role in determining the size and direction of incremental costs when comparing participants with

PIP versus those without. This is not surprising though given the medication costs were a constant for all individuals with a PIP (or no PIP in the case of START A6).

To place the incremental cost results obtained from each PIP case-study into context, we captured the incremental costs due to any PIP from hospitalizations and ED visits for the entire cohort of participants form a previously conducted study (Chapter 3). This is essentially an estimate of the average health system cost from all criteria applicable to HAD in Ontario. In the entire cohort, the adjusted mean incremental costs due to any PIP in a cohort of 2.27 million people was $184.61 (95% CI: 179.07 to 190.15) with a cost ratio of 2.18.

The PIPs selected as cases for our present study were chosen because they varied by frequency and crude cost (from hospitalization, ED visit and PIP medication). START A6, defined as the omission of an angiotensin converting enzyme (ACE) inhibitor with systolic heart failure and/or documented coronary artery disease, was classified as having a high frequency of occurrence and had moderate crude costs, while STOPP K2, the prescribing of any neuroleptic drug, was classified as moderate in both frequency and crude costs. STOPP D8, defined as anticholinergics/antimuscarinics in patients with delirium or dementia, and STOPP J6, defined as androgens in the absence of primary and secondary hypogonadism, were both classified as low frequency, but were on opposite sides of the crude cost classifications at high and low crude costs, respectively.

Generally, the incremental cost estimates aligned with the crude cost classifications for each PIP. The two PIPs with positive incremental costs from our present study, STOPP D8 and STOPP K2, had adjusted mean incremental cost estimates that mirrored their crude cost groupings on either side of the average incremental costs of any PIP described above, and these results are

likely due to the nature and definition of each PIP. STOPP D8, by definition, applies to participants with delirium or dementia and is concerned with placing a person at increased risk of falls, while STOPP K2 applies more generally to the entire population, some of whom may not be at as high of a risk of a negative outcome as patients with dementia. The non-significant incremental cost findings for STOPP J6 are in line with its crude cost classification, as it had the lowest crude costs. The incremental costs for START A6 are at odds with its crude cost classification, though this is likely due to the time period over which costs were captured. The crude costs to determine the classifications were based on all costs following a PIP, with no restriction on the time period. Given that treatment with an ACE inhibitor is likely to impact outcomes such as hospitalizations and ED visits beyond the 90-day observation window used in our study, we hypothesize that the incremental costs for participants with the START A6 PIP would be greater than those without a PIP over a longer time horizon.

The secondary outcomes of this study, namely incremental costs from hospitalizations and ED visits individually, as well as total health system costs from hospitalizations, ED visit and PIP medication due to each PIP for all participants combined based on the PIP's prevalence, provide additional information on the drivers of PIP related costs. While the incremental costs for these categories were not large in magnitude and may not appear to be clinically significant, they do provide information on the direction of effect and drivers of cost. The largest individual factor on combined incremental costs varied by the case-study PIPs with positive incremental costs. For STOPP D8, ED visits appeared to be the driver, while for STOPP K2, hospitalization costs were a larger factor. In each of these two cases, the cost of the drug appeared to be as large of a contributor as hospitalization costs or ED visits, while for STOPP J6, costs from ED visits and hospitalizations, which were lower in participants with the PIP, were offset by a high drug cost,

indicating that the cost of the drug is a large factor in the costs from PIP. Additionally, looking at these costs by category and observing their magnitude and direction of effect highlights the importance of looking at incremental costs of specific PIP. While in general all PIP combined contribute to increased hospitalizations and ED visit costs, the negative and non-significant incremental costs obtained in some categories show that not all PIPs contribute to these costs equally and may not necessarily need to be prioritized given their impact.

The estimates for total health system costs from each person with the PIP of interest outline the importance of the PIP frequency on the burden of the individual PIP on the healthcare system. While participants with STOPP D8 had much higher mean incremental costs due to PIP when compared with participants with STOPP K2, STOPP K2 had nearly double the total costs due to PIP based on its much higher prevalence. The results from this analysis also point to the importance of considering the whole population who might be affected by a PIP when determining priorities. While we selected patients experiencing a PIP as their first PIP ever, without any additional overlapping PIP, within our primary analyses, the reality is that there are many more individuals experiencing each PIP as either their second PIP or beyond.

Our study is subject to some limitations common to observational research using routinely collected health-administrative databases whose original collection was not for research purposes. As with all observational studies, the results only report on potential associations between the PIPs modelled and their health system costs and are not a proof of causality. There is also the potential for some residual confounding that we were unable to address, particularly by indication which is common in medication studies, though we are confident that we have identified all potentially important confounding variables available to us without overfitting our models and that our conservative estimates display the true direction of effect. Additionally, we

are only capturing the costs from the 90-day period after the first time a PIP occurred for each criterion, so we do not have costs for each time the same PIP was repeated for each person, or when it was a PIP for someone with a different first PIP ever. While a limitation on the true estimate of the incremental costs of each PIP, it likely means we are underestimating the costs of PIP, as described above. In addition to obtaining conservative estimates, our study used the best practices for econometric model building and analyses, as outlined in the literature [18–21].

4.2.6 Conclusion

The incremental costs due to PIP from hospitalizations, ED visits and PIP medications varied by the criterion studied, yet generally matched their classification based on crude costs. Additionally, drug costs appeared to be a large component of the incremental costs in each case, while the prevalence of the PIP played a large role in determining the total estimated costs to the healthcare system from all persons experiencing a PIP combined. These results indicate that the PIP's prevalence and its crude costs may be the best characteristics to identify a PIP's potential impacts to the healthcare system. Such characteristics may be efficient for use by healthcare decision makers to determine priority PIPs for intervention without having to conduct large scale studies on every single PIP criterion, instead allowing for resources to be diverted towards interventions. Further research should aim to confirm these findings on a larger sample of PIP criteria, as well as to evaluate the implementation of interventions to address PIP which place a large burden on the Canadian healthcare system.

4.2.7 References for Chapter 4

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4.2.8 Tables and figures for Chapter 4

Table 6. Definitions for PIP criteria under study, along with their frequency and crude cost classification

PIP	Definition[12]	Frequency Grouping	Cost Grouping
START A6	Angiotensin Converting Enzyme (ACE) inhibitor with systolic heart failure and/or documented coronary artery disease	High	Mid
STOPP K2	Neuroleptic drugs (may cause gait dyspraxia, Parkinsonism)	Mid	Mid
STOPP D8	Anticholinergics/antimuscarinics in patients with delirium or dementia (risk of exacerbation of cognitive impairment)	Low	High
STOPP J6	Androgens (male sex hormones) in the absence of primary or secondary hypogonadism (risk of androgen toxicity; no proven benefit outside of the hypogonadism indication).	Low	Low

Table 7. Unadjusted and adjusted costs of medical expenditures with PIP vs. without from hospitalizations, ED visits and medications (CAD$2017)

PIP Criteria	Drug costs* ($)	Unadjusted mean costs ($) (SD)		Adjusted mean costs ($) (SD)		Adjusted incremental costs ($) (95% CI)	Cost ratio
		with PIP	without PIP	with PIP	without PIP		
START A6 (n=228,272)	-15.30	1099.09 (6141.37)	798.10 (4867.39)	327.02 (19512.91)	299.01 (19943.52)	28.00 (-133.86 to 189.87)	1.09
STOPP D8 (n=1,241)	27.00	3350.32 (8033.09)	1595.18 (7216.02)	1207.26 (1880.82)	968.75 (1550.11)	238.51 (47.62 to 429.40)	1.25
STOPP J6 (n=10,190)	126.90	422.65 (2997.58)	205.39 (3029.42)	150.16 (3362.65)	159.26 (3740.79)	-9.10 (-147.02 to 128.82)	0.94
STOPP K2 (n=6544)	23.40	752.67 (3587.59)	175.07 (2487.78)	152.62 (497.07)	83.9 (272.52)	68.66 (50.01 to 87.31)	1.82

95% CI – 95% confidence interval; PIP – potentially inappropriate prescription; START – screening tool to alert to right treatment; STOPP – screening tool of older people's prescriptions

*Medication costs were fixed based on cheapest available alternative in class based on PrescribeSmart app and WHO DDD

Table 8. Total costs associated with each PIP from hospitalization, ED visits and medication costs, as the first PIP ever or at any point (in CAD$2017)

PIP Criteria	Adjusted incremental costs ($) (95% CI)	First PIP ever		PIP at any time	
		Number of persons with PIP	Total costs ($) (95% CI)*	Number of persons with PIP	Total costs ($) (95% CI)*
START A6	28.00 (-133.86 to 189.87)	216,054	6,050,030 (-28,921,114 to 41,021,175)	717,119	20,081,053 (-95,993,967 to 136,156,073)
STOPP D8	238.51 (47.62 to 429.40)	729	173,876 (34,718 to 313,034)	49,792	11,876,044 (2,371,297 to 21,380,792)
STOPP J6	-9.10 (-147.02 to 128.82)	5,246	-47,748 (-771,293 to 675,798)	13,754	-125,185 (-2,022,181 to 1,771,811)
STOPP K2	68.66 (50.01 to 87.31)	3,421	234,883 (171,094 to 298,672)	258,617	17,756,441 (12,934,182 to 22,578,701)

95% CI – 95% confidence interval; PIP – potentially inappropriate prescription; START – screening tool to alert to right treatment; STOPP – screening tool of older people's prescriptions

*Calculated by multiplying number of persons with PIP by the incremental costs; range obtained by multiplying number of persons with PIP by lower and upper bound of 95% Confidence Interval

Table 9. Source of expenditure by PIP (in CAD$2017)

PIP Criteria	Median prescription medications costs ($) (Range*)	Adjusted mean incremental costs from hospitalizations ($)	Adjusted mean incremental costs from ED visits ($)
START A6			
PIP	0	148.30 (2450.89)	13.84 (44.81)
No PIP	30.38 (15.30 to 97.20)	135.47 (2451.36)	11.14 (36.72)
Difference (95%CI)	-30.38 (-15.30 to -97.20)	12.83 (-7.65 to 33.31)	2.70 (2.36 to 3.03)
STOPP D8			
PIP	94.5 (27.00 to 145.80)	881.11 (1607.62)	34.73 (79.01)
No PIP	0	867.37 (1633.12)	16.89 (38.02)
Difference	94.5 (27.00 to 145.80)	13.73 (-166.58 to 194.04)	18.84 (12.33 to 25.35)
STOPP J6			
PIP	452.45 (126.90 to 777.60)	24.81 (649.59)	2.53 (13.65)
No PIP	0	26.24 (691.21)	21.17 (115.30)
Difference	452.45 (126.90 to 777.60)	-1.43 (-27.48 to 24.63)	-18.64 (-21.14 to -16.14)
STOPP K2			
PIP	115.20 (23.4 to 712.80)	74.64 (385.98)	10.78 (35.41)
No PIP	0	48.90 (280.93)	5.17 (17.32)
Difference	115.20 (23.4 to 712.80)	25.74 (9.58 to 41.90)	5.61 (4.33 to 6.89)

ED – emergency department; PIP – potentially inappropriate prescription; START – screening tool to alert to right treatment; STOPP – screening tool of older people's prescriptions

*Medication costs were fixed based on cheapest available alternative in class, as well as the median and highest costs, based on PrescribeSmart app and WHO DDD

4.2.9 Supplement for Chapter 4

Supplement A

Table A. The RECORD statement – checklist of items, extended from the STROBE statement

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	77	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	77 79 79

Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	80-81		
Objectives	3	State specific objectives, including any prespecified hypotheses	81		
Methods					
Study Design	4	Present key elements of study design early in the paper	82		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	82		
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case	82	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided.	82-84 82-84

		ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case		RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	Decided against including this type of graphic besides study flow diagrams presented in the supplementary materials
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and	82-84, Supplement C	RECORD 7.1: A complete list of codes and algorithms used to classify exposures,	83-84, greater detail on coding and instructions referenced in a prior

		effect modifiers. Give diagnostic criteria, if applicable.		outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	protocol
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	84 - Described in a referenced protocol		
Bias	9	Describe any efforts to address potential sources of bias	Described in the referenced study protocol		
Study size	10	Explain how the study size was arrived at	N/A – based on eligibility criteria solely		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	Described in referenced study protocol		
Statistical	12	(a) Describe all statistical	85-86		

methods		methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses			
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to	Previously reported in referenced study protocol

				the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	82
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included	86-87	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based	86

		in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram		on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	86-87 116-117 in supplementary tables NA		
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure	NA		

		category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	87 Confounder adjusted estimates: 87-88		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and	88-89		

		interactions, and sensitivity analyses			
Discussion					
Key results	18	Summarise key results with reference to study objectives	90		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	93-94	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	93-94
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	91-93		

Generalisability	21	Discuss the generalisability (external validity) of the study results	94		
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	5		
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	N/A given data source, protocol referenced in methods section (pg. 44)

Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

Supplement B

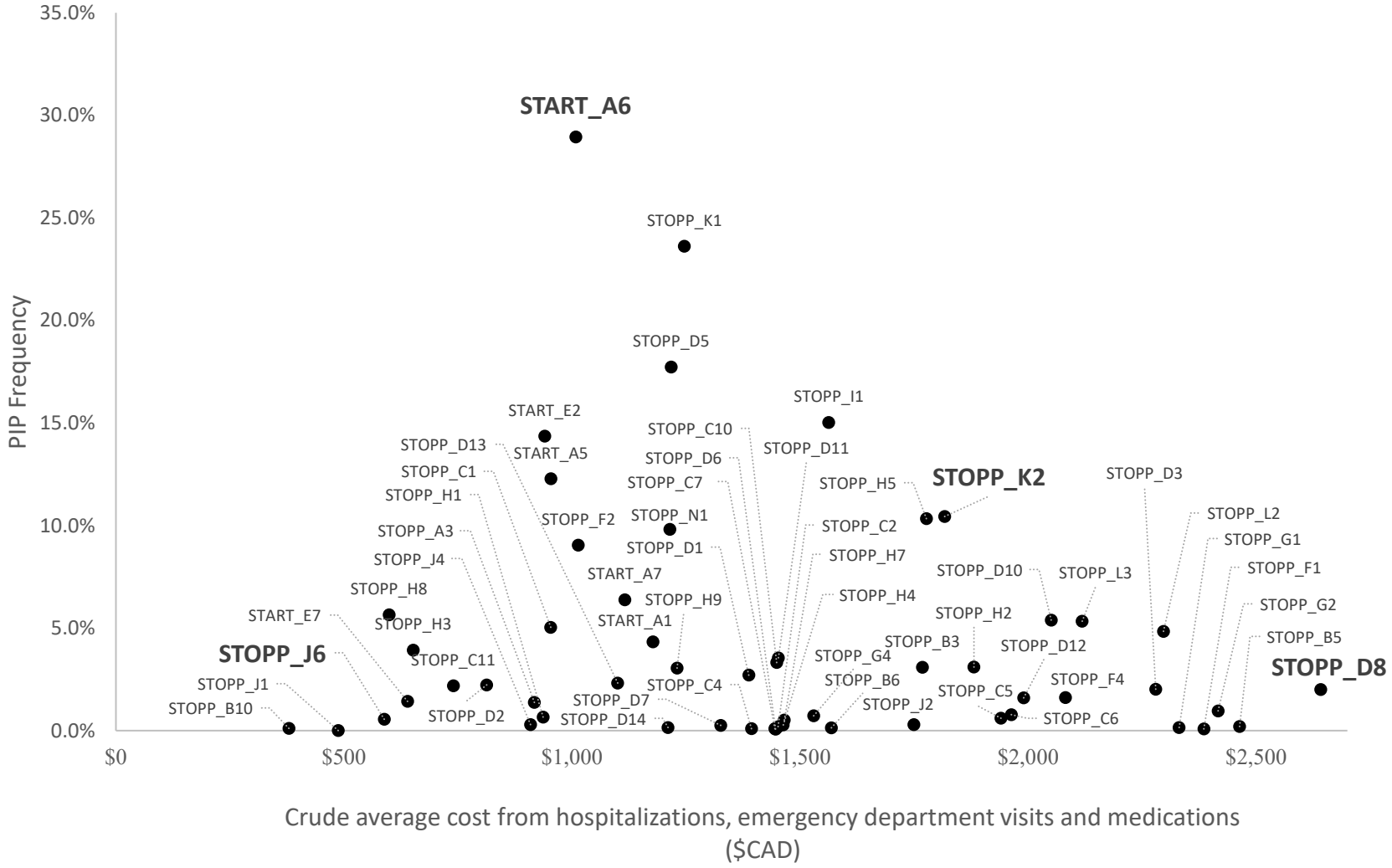

Figure A. Assessment of PIP frequency by crude costs (from hospitalizations, emergency department visits and medications) to determine PIP scenarios to be modelled

Supplement C

We identified the status as of PIP index date of a number of covariates that were either associated with PIP or the outcome of interest that could be confounding variables to be included in all statistical analyses: age [42,43], sex [43], income quintile [43,44], rurality, aggregated diagnosis group (ADG) score (i.e. comorbidity status) [43,45,46], number of unique drug identification numbers (i.e. pills prescribed concurrently) in year prior to PIP [47–51], number of prescribers in year prior to PIP [52], whether the patient had a MedsCheck (billable medication review performed by a pharmacist, usually in the community) in year prior to PIP, number of days spent in hospital in year prior to PIP, and ED visit in 6 months prior to PIP [42,43,45,53–57].

Supplement D

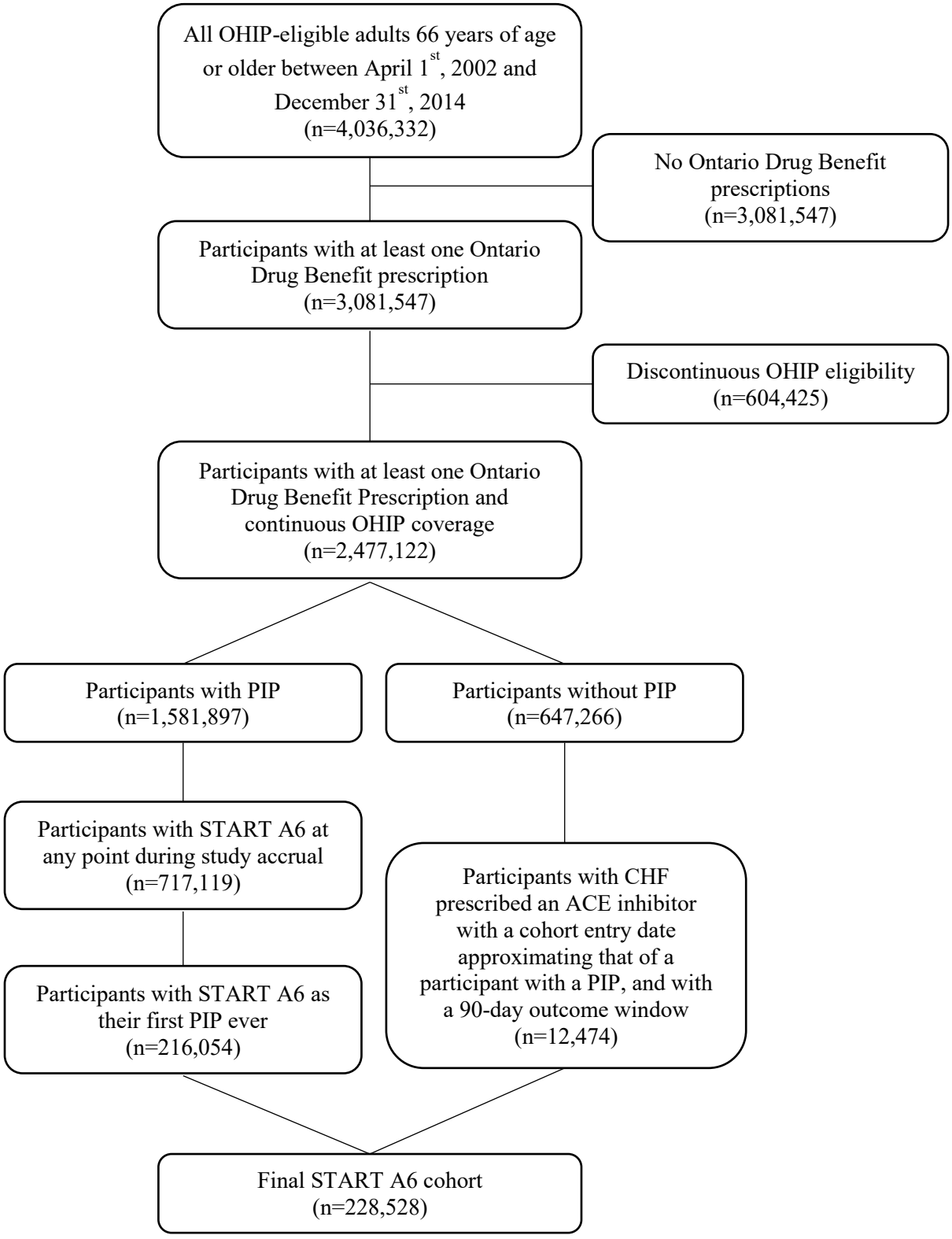

Figure A. START A6 cohort creation steps

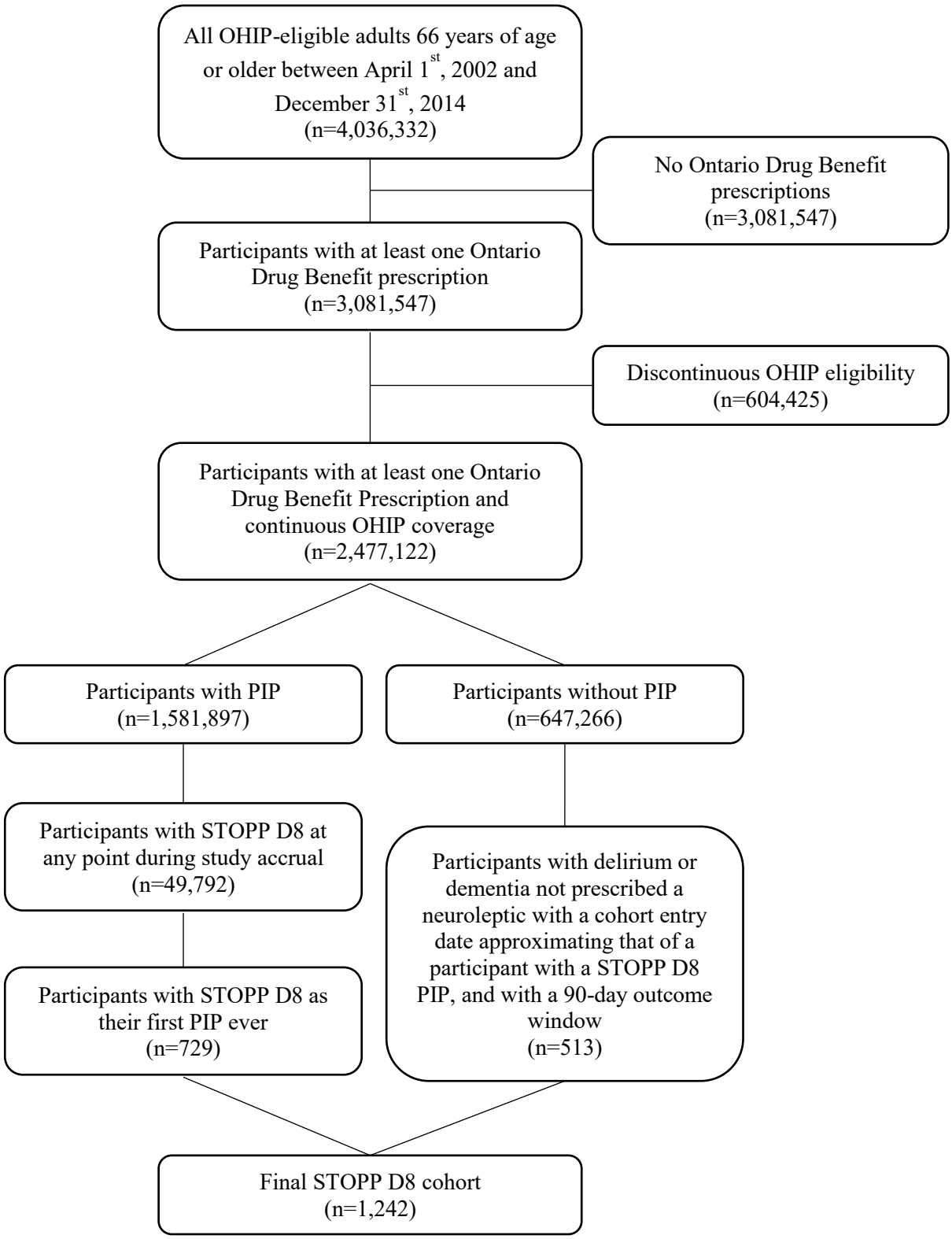

Figure B. STOPP D8 cohort creation steps

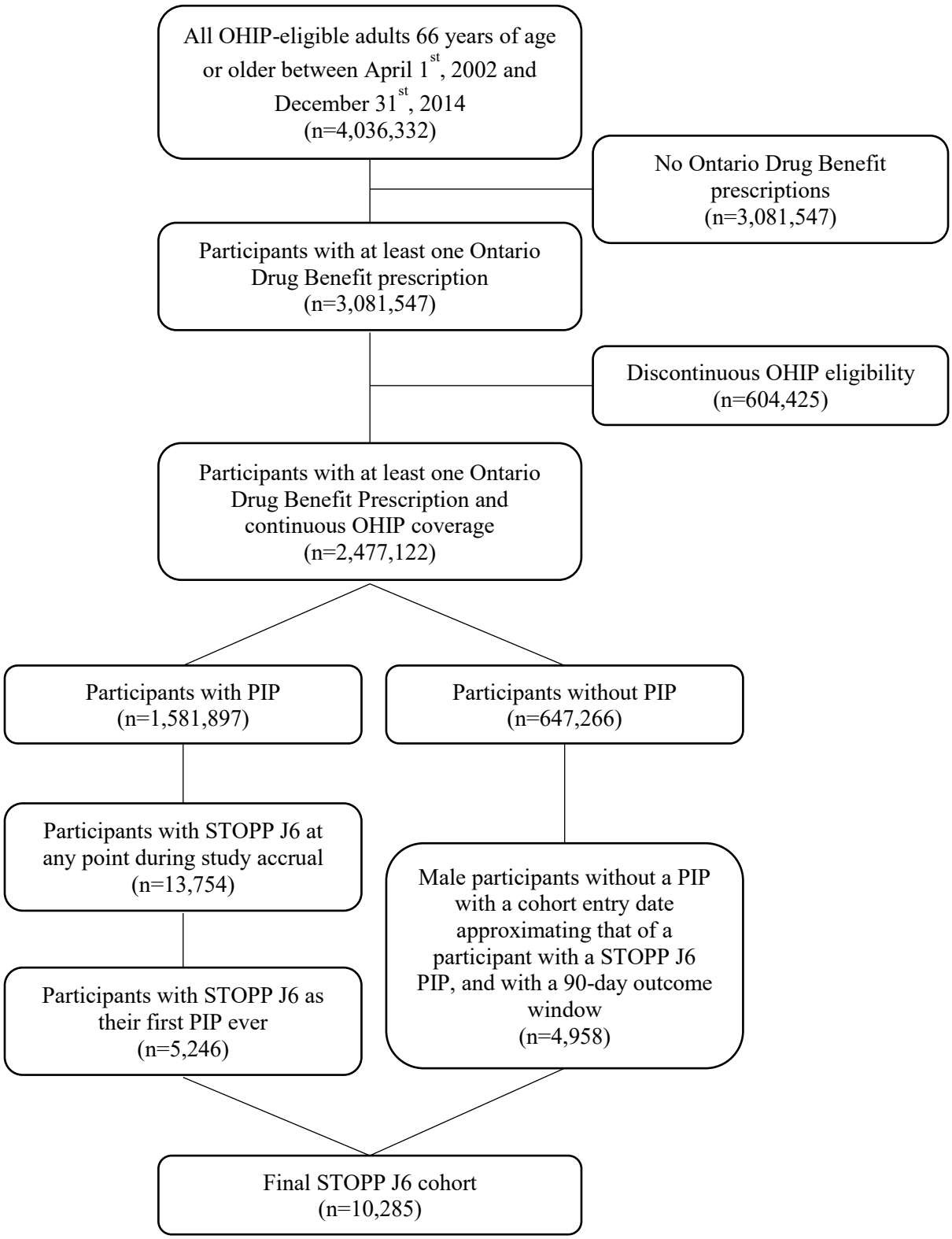

Figure C. STOPP J6 cohort creation steps

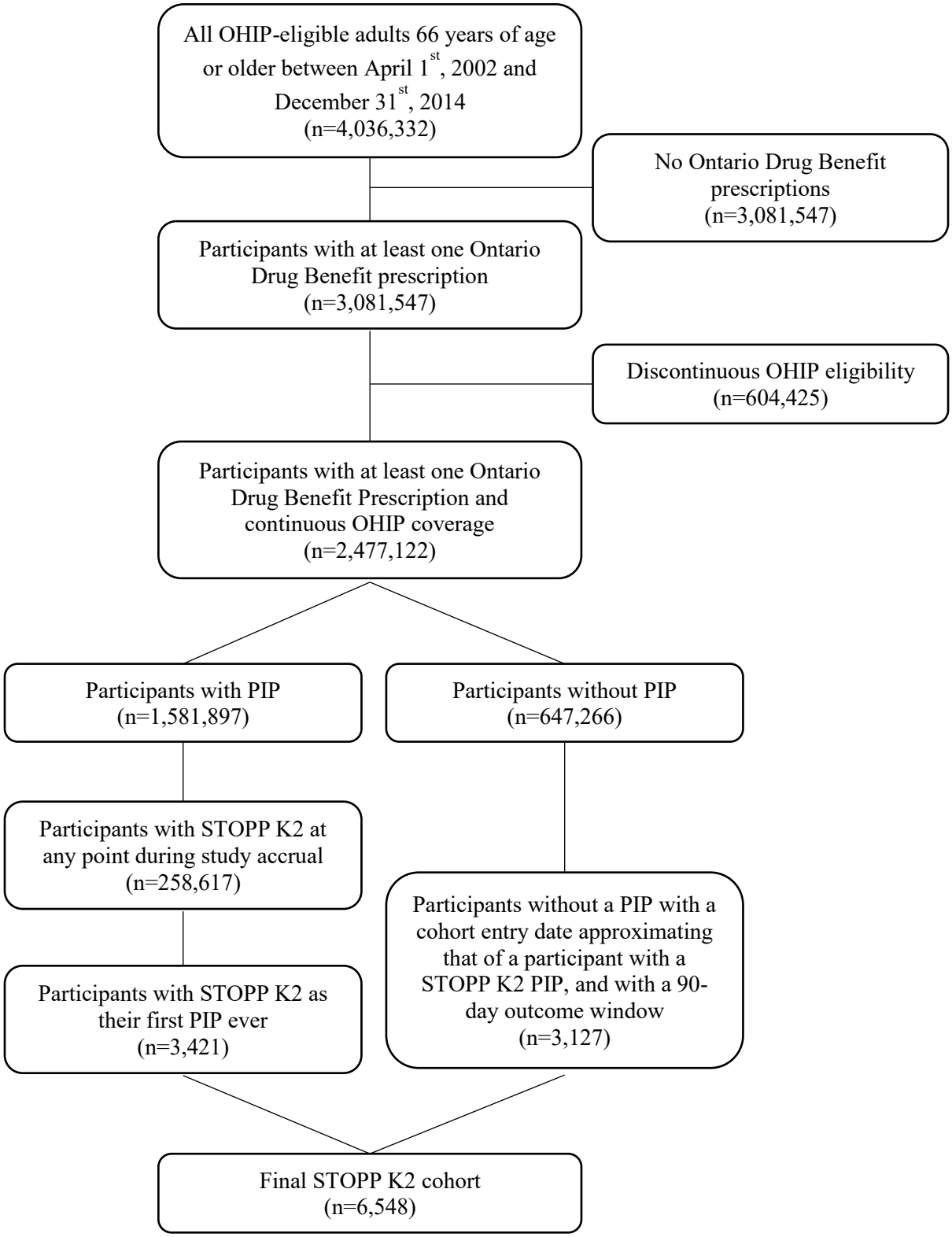

Figure D. STOPP K2 cohort creation steps

Supplement E

Table A. Criterion-specific study population characteristics

CHARACTERISTIC	Had PIP	No PIP	OVERALL
START A6	N=216,054	N=12,474	N=228,528
Mean age (SD)	75.1 (7.9)	73.6 (7.3)	75.5 (7.9)
Sex (male)	58.5%	54.9%	58.3%
Number of ADGs (SD)	9.3 (3.6)	6.7 (3.6)	9.3 (3.6)
Number of concurrent meds (SD)	5.1 (2.8)	2.5 (2.3)	5.1 (2.7)
Mean number of days spent in hospital in year prior to 1st PIP or assigned PIP date (SD)	4.2 (10.1)	1.0 (6.2)	4.5 (10.8)
≥1 ED visits in 6 months prior to 1st PIP or assigned PIP date	38.0%	33.3%	24.8%
Income quintile			
1 - lowest	19.5%	17.6%	19.4%
2	21.3%	20.8%	21.3%
3	19.8%	20.5%	19.8%
4	19.4%	20.9%	19.5%
5 - highest	19.7%	19.8%	19.7%
Missing	0.4%	0.4%	0.4%
Place of residence (urban)	85.0%	86.9%	85.1%
Number of prescribers in the year prior to first PIP (SD)	2.9 (1.7)	1.9 (1.3)	3.0 (1.7)
MedsCheck in year prior	6.3%	20.4%	7.1%
STOPP D8	N=729	N=513	N=1,242
Mean age (SD)	80.3 (8.4)	81.2 (7.1)	80.7 (8.6)
Sex (male)	32.4%	33.9%	33.0%
Number of ADGs (SD)	12.1 (3.8)	8.4 (3.8)	10.8 (4.1)
Number of concurrent meds (SD)	6.5 (3.2)	2.9 (2.6)	5.0 (3.5)
Mean number of days spent in hospital in year prior to 1st PIP or assigned PIP date (SD)	14.3 (23.8)	4.6 (12.0)	10.3 (20.4)
≥1 ED visits in 6 months prior to 1st PIP or assigned PIP date	74.9%	34.9%	58.4%
Income quintile			
1 - lowest	22.9%	20.3%	21.8%
2	23.5%	20.3%	22.1%
3	15.6%	20.7%	17.7%
4	17.4%	18.1%	17.7%
5 - highest	20.3%	20.5%	20.4%
Missing	0.3%	0.2%	0.2%
Place of residence (urban)	88.1%	87.1%	87.7%

Number of prescribers in the year prior to first PIP (SD)	3.1 (2.7)	2.2 (1.9)	2.8 (2.4)
MedsCheck in year prior	10.8%	8.6%	9.9%
STOPP J6	N=5,246	N=4,958	N=10,285
Mean age (SD)	69.0 (4.5)	69.7 (5.2)	68.8 (5.1)
Number of ADGs (SD)	8.2 (3.4)	6.0 (3.3)	7.1 (3.6)
Number of concurrent meds (SD)	4.0 (2.5)	3.0 (2.5)	3.0 (2.5)
Mean number of days spent in hospital in year prior to 1st PIP or assigned PIP date (SD)	0.5 (3.5)	0.6 (5.1)	0.5 (4.3)
≥1 ED visits in 6 months prior to 1st PIP or assigned PIP date	11.4%	9.8%	10.6%
Income quintile			
1 - lowest	14.0%	15.8%	14.9%
2	17.9%	19.0%	18.5%
3	18.7%	20.0%	19.4%
4	21.0%	20.3%	20.7%
5 - highest	28.0%	24%	26.1%
Missing	0.5%	0.6%	0.5%
Place of residence (urban)	85.5%	84.6%	85.1%
Number of prescribers in the year prior to first PIP (SD)	2.2 (1.9)	2.0 (1.7)	2.0 (1.7)
MedsCheck in year prior	10.7%	8.2%	8.8%
STOPP K2	N=3,421	N=3,127	N=6,548
Mean age (SD)	73.0 (9.2)	70.3 (6.8)	71.7 (8.2)
Sex (male)	29.4%	43.1%	36.0%
Number of ADGs (SD)	9.1 (4.1)	6.4 (3.4)	7.8 (4.0)
Number of concurrent meds (SD)	5.1 (3.0)	2.5 (2.1)	3.9 (2.9)
Mean number of days spent in hospital in year prior to 1st PIP or assigned PIP date (SD)	4.1 (14.9)	0.5 (3.0)	2.4 (11.1)
≥1 ED visits in 6 months prior to 1st PIP or assigned PIP date	34.1%	9.3%	22.3%
Income quintile			
1 - lowest	24.6%	17.4%	21.2%
2	20.2%	21.1%	20.6%
3	19.4%	18.8%	19.1%
4	17.8%	20.7%	19.2%
5 - highest	17.7%	21.6%	19.6%
Missing	0.3%	0.4%	0.4%
Place of residence (urban)	88.5%	85.8%	87.2%
Number of prescribers in the year prior to first PIP (SD)	2.6 (2.1)	1.8 (1.5)	2.2 (1.9)
MedsCheck in year prior	9.5%	5.8%	7.7%

Supplement F

Table A. Model output – primary analysis, START A6

	Logistic Regression		GLM	
	Number of observations	228,272	**Number of observations**	35,477
	Dependent variable	Any costs from ED visit or hospitalization (Yes/No)	**Dependent variable**	Combined costs from ED visits and hospitalizations
Model variables	**Coefficient**	**SE**	**Coefficient**	**SE**
Intercept	-3.7645	0.0659	8.3442	0.0967
Had a PIP	0.1192	0.0148	-0.0457	0.0400
Age (continuous)	0.0130	0.000785	0.0026	0.0011
Sex female (ref male)	0.0342	0.00625	0.2152	0.0164
ADG count (continuous)	0.0659	0.00188	-0.0268	0.0024
Did not have a MedsCheck	-0.0654	0.0122	0.0913	0.0320
Number of prescribers	0.0627	0.00362	0.0080	0.0046
Lived in an urban setting (ref rural)	-0.1898	0.00779	0.2560	0.0200
Number of unique medications at index date (continuous)	0.0417	0.00212	0.0050	0.0026
ED visit in six months prior to index date (ref is no)	0.2739	0.00654	-0.0314	0.0176
Number of days spent in hospital in year prior to index (continuous)	0.0124	0.000477	0.0202	0.0006
Income quintile 1 – Lowest	0.0538	0.00947	-0.0594	0.0249
Income quintile 2	0.0320	0.00937	-0.0392	0.0247
Income quintile 3	0.0174	0.00959	-0.0152	0.0254
Income quintile 4 – 4th highest (ref is highest)	0.00518	0.00969	0.0298	0.0257
Scale	NA	NA	0.4605	0.0028

Table B. Model output – primary analysis, STOPP D8

	Logistic Regression		GLM	
	Number of observations	1,241	**Number of observations**	415
	Dependent variable	Any costs from ED visit or hospitalization (Yes/No)	**Dependent variable**	Combined costs from ED visits and hospitalizations
Model variables	**Coefficient**	**SE**	**Coefficient**	**SE**
Intercept	-2.3372	0.7161	7.6486	0.8995
Had a PIP	0.4024	0.0841	-0.2393	0.2015
Age (continuous)	0.0181	0.00797	0.0148	0.0094
Sex female (ref male)	0.0608	0.0718	-0.0275	0.1577
ADG count (continuous)	0.0294	0.0189	-0.0016	0.0201
Did not have a MedsCheck	0.0339	0.1129	0.3851	0.2528
Number of prescribers	-0.0670	0.0302	-0.0242	0.0330
Lived in an urban setting (ref rural)	-0.1955	0.0994	0.1722	0.2088
Number of unique medications at index date (continuous)	0.0511	0.0218	0.0038	0.0242
ED visit in six months prior to index date (ref is no)	0.6031	0.0791	0.2217	0.1846
Number of days spent in hospital in year prior to index (continuous)	-0.00112	0.00326	-0.0003	0.0039
Income quintile 1 – Lowest	0.1073	0.1015	-0.0043	0.2198
Income quintile 2	0.1393	0.1015	-0.0543	0.2149
Income quintile 3	0.1352	0.1091	-0.0967	0.2359
Income quintile 4 – 4th highest (ref is highest)	0.1400	0.1081	-0.1199	0.2310
Scale	NA	NA	0.5343	0.0308

Table C. Model output – primary analysis, STOPP J6

	Logistic Regression		GLM	
	Number of observations	10,190	**Number of observations**	747
	Dependent variable	Any costs from ED visit or hospitalization (Yes/No)	**Dependent variable**	Combined costs from ED visits and hospitalizations
Model variables	**Coefficient**	**SE**	**Coefficient**	**SE**
Intercept	-4.4518	0.5182	5.9833	0.7539
Had a PIP	0.00820	0.0439	-0.1070	0.1399
Age (continuous)	0.0247	0.00711	0.0213	0.0109
ADG count (continuous)	0.0713	0.0120	0.4755	0.1494
Did not have a MedsCheck	0.00438	0.0669	-0.2569	0.2054
Number of prescribers	-0.00968	0.0233	0.0106	0.0361
Lived in an urban setting (ref rural)	-0.2413	0.0484	-0.0092	0.0182
Number of unique medications at index date (continuous)	0.0524	0.0166	0.1304	0.0260
ED visit in six months prior to index date (ref is no)	0.3991	0.0500	0.3004	0.1611
Number of days spent in hospital in year prior to index (continuous)	0.0288	0.00678	0.0238	0.0064
Income quintile 1 – Lowest	0.0960	0.0613	-0.6148	0.1891
Income quintile 2	0.0407	0.0592	-0.4436	0.1774
Income quintile 3	0.0220	0.0589	-0.4852	0.1758
Income quintile 4 – 4th highest (ref is highest)	-0.00423	0.0591	-0.3754	0.1788
Scale	NA	NA	0.4375	0.0185

Table D. Model output – primary analysis, STOPP K2

	Logistic Regression		GLM	
	Number of observations	6,544	**Number of observations**	921
	Dependent variable	Any costs from ED visit or hospitalization (Yes/No)	**Dependent variable**	Combined costs from ED visit and hospitalization
Model variables	**Coefficient**	**SE**	**Coefficient**	**SE**
Intercept	-3.4376	0.3535	5.3242	0.4951
Had a PIP	0.2619	0.0473	0.3282	0.1257
Age (continuous)	0.0138	0.00461	0.0259	0.0062
Sex female (ref male)	-0.00351	0.0416	0.1722	0.1100
ADG count (continuous)	0.0712	0.0108	0.0394	0.0146
Did not have a MedsCheck	-0.1687	0.0811	-0.0122	0.2120
Number of prescribers	0.00984	0.0204	0.0217	0.0253
Lived in an urban setting (ref rural)	-0.1061	0.0552	-0.0420	0.1470
Number of unique medications at index date (continuous)	0.0106	0.0142	0.0071	0.0179
ED visit in six months prior to index date (ref is no)	0.4653	0.0418	-0.1744	0.1084
Number of days spent in hospital in year prior to index (continuous)	0.0201	0.00308	0.0003	0.0027
Income quintile 1 – Lowest	0.0916	0.0588	0.4866	0.1494
Income quintile 2	-0.00940	0.0616	0.1626	0.1618
Income quintile 3	0.0576	0.0618	-0.3263	0.1586
Income quintile 4 – 4th highest (ref is highest)	0.0232	0.0621	-0.0595	0.1644
Scale	NA	NA	0.4850	0.0186

Table E. Model output – secondary analysis of ED visits only, START A6

	Logistic Regression		GLM	
	Number of observations	228,272	**Number of observations**	29,584
	Dependent variable	Any costs from ED visit (Yes/No)	**Dependent variable**	Costs from ED visits
Model variables	**Coefficient**	**SE**	**Coefficient**	**SE**
Intercept	-4.4526	0.0709	5.1415	0.0514
Had a PIP	0.1318	0.0162	0.0095	0.0222
Age (continuous)	0.0188	0.000838	0.0092	0.0006
Sex female (ref male)	0.000948	0.00669	0.0396	0.0088
ADG count (continuous)	0.0710	0.00201	0.0015	0.0013
Did not have a MedsCheck	-0.0647	0.0132	-0.0005	0.0175
Number of prescribers	0.0656	0.00386	0.0132	0.0024
Lived in an urban setting (ref rural)	-0.2140	0.00825	0.1380	0.0108
Number of unique medications at index date (continuous)	0.0554	0.00225	0.0204	0.0014
ED visit in six months prior to index date (ref is no)	0.3067	0.00703	0.1059	0.0096
Number of days spent in hospital in year prior to index (continuous)	0.00345	0.000513	0.0204	0.0014
Income quintile 1 – Lowest	0.0841	0.0102	0.0370	0.0136
Income quintile 2	0.0574	0.0101	0.0353	0.0136
Income quintile 3	0.0378	0.0104	0.0194	0.0140
Income quintile 4 – 4th highest (ref is highest)	0.0176	0.0106	0.0215	0.0142
Scale	NA	NA	1.8569	0.0141

Table F. Model output – secondary analysis of ED visits only, STOPP D8

	Logistic Regression		GLM	
	Number of observations	1,241	**Number of observations**	248
	Dependent variable	Any costs from ED visit (Yes/No)	**Dependent variable**	Costs from ED visits
Model variables	**Coefficient**	**SE**	**Coefficient**	**SE**
Intercept	-1.7125	0.7947	4.7144	0.5186
Had a PIP	0.3810	0.0973	0.1552	0.1196
Age (continuous)	0.00222	0.00891	0.0106	0.0057
Sex female (ref male)	0.0211	0.0797	0.0458	0.1006
ADG count (continuous)	0.0294	0.0208	0.0185	0.0129
Did not have a MedsCheck	0.0619	0.1208	0.1581	0.1545
Number of prescribers	0.00849	0.0305	0.0042	0.0193
Lived in an urban setting (ref rural)	-0.2040	0.1060	0.1641	0.1275
Number of unique medications at index date (continuous)	0.0400	0.0238	0.0172	0.0164
ED visit in six months prior to index date (ref is no)	0.1609	0.0873	0.1738	0.1091
Number of days spent in hospital in year prior to index (continuous)	-0.0106	0.00480	0.0069	0.0034
Income quintile 1 – Lowest	0.1592	0.1135	0.1375	0.1460
Income quintile 2	0.0430	0.1161	-0.0623	0.1470
Income quintile 3	0.1010	0.1231	0.0367	0.1562
Income quintile 4 – 4th highest (ref is highest)	0.1485	0.1203	-0.1026	0.1522
Scale	NA	NA	2.0705	0.1730

Table G. Model output – secondary analysis of ED visits only, STOPP J6

	Logistic Regression		GLM	
	Number of observations	10190	**Number of observations**	659
	Dependent variable	Any costs from ED visit (Yes/No)	**Dependent variable**	Costs from ED visits
Model variables	**Coefficient**	**SE**	**Coefficient**	**SE**
Intercept	-4.7556	0.5427	5.4099	0.3384
Had a PIP	0.0141	0.0463	0.0700	0.0620
Age (continuous)	0.0261	0.00744	0.0062	0.0048
ADG count (continuous)	0.0723	0.0126	-0.0050	0.0080
Did not have a MedsCheck	0.00539	0.0701	0.0988	0.0936
Number of prescribers	0.00169	0.0242	-0.0042	0.0152
Lived in an urban setting (ref rural)	-0.2555	0.0506	0.2081	0.0680
Number of unique medications at index date (continuous)	0.0523	0.0174	0.0320	0.0110
ED visit in six months prior to index date (ref is no)	0.4002	0.0524	0.0230	0.0681
Number of days spent in hospital in year prior to index (continuous)	0.00703	0.00543	0.0063	0.0028
Income quintile 1 – Lowest	0.0707	0.0643	-0.4081	0.0860
Income quintile 2	0.0294	0.0617	-0.2119	0.0825
Income quintile 3	-0.00200	0.0617	-0.2361	0.0831
Income quintile 4 – 4th highest (ref is highest)	-0.0499	0.0627	-0.0821	0.0841
Scale	NA	NA	2.0813	0.1067

Table H. Model output – secondary analysis of ED visits only, STOPP K2

	Logistic Regression		GLM	
	Number of observations	6,544	**Number of observations**	731
	Dependent variable	Any costs from ED visit (Yes/No)	**Dependent variable**	Costs from ED visit
Model variables	**Coefficient**	**SE**	**Coefficient**	**SE**
Intercept	-3.3688	0.3788	5.6058	0.2668
Had a PIP	0.2431	0.0503	0.3390	0.0682
Age (continuous)	0.0116	0.00494	0.0007	0.0034
Sex female (ref male)	0.0211	0.0441	-0.0066	0.0614
ADG count (continuous)	0.0830	0.0115	0.0092	0.0074
Did not have a MedsCheck	-0.1015	0.0833	0.1582	0.1118
Number of prescribers	0.0193	0.0217	-0.0279	0.0136
Lived in an urban setting (ref rural)	-0.1514	0.0575	0.2062	0.0774
Number of unique medications at index date (continuous)	0.000726	0.0152	0.0079	0.0100
ED visit in six months prior to index date (ref is no)	0.3196	0.0455	0.1056	0.0612
Number of days spent in hospital in year prior to index (continuous)	0.000792	0.00292	-0.0002	0.0019
Income quintile 1 – Lowest	0.1381	0.0637	0.0194	0.0851
Income quintile 2	0.0235	0.0671	-0.0240	0.0926
Income quintile 3	0.0989	0.0668	-0.0336	0.0898
Income quintile 4 – 4th highest (ref is highest)	0.1023	0.0665	-0.0450	0.0899
Scale	NA	NA	1.9117	0.0926

Table I. Model output – secondary analysis of hospitalization only, START A6

	Logistic Regression		GLM	
	Number of observations	228,272	**Number of observations**	17,907
	Dependent variable	Any costs from hospitalization (Yes/No)	**Dependent variable**	Combined costs from hospitalizations
Model variables	**Coefficient**	**SE**	**Coefficient**	**SE**
Intercept	-5.0200	0.0884	9.8988	0.0793
Had a PIP	0.1022	0.0203	-0.0540	0.0329
Age (continuous)	0.0185	0.00104	-0.0061	0.0009
Sex female (ref male)	0.0947	0.00842	0.1074	0.0134
ADG count (continuous)	0.0422	0.00251	-0.0131	0.0020
Did not have a MedsCheck	-0.0931	0.0166	0.1793	0.0265
Number of prescribers	0.0557	0.00475	0.0033	0.0037
Lived in an urban setting (ref rural)	-0.0402	0.0110	0.0543	0.0175
Number of unique medications at index date (continuous)	0.0496	0.00275	-0.0161	0.0020
ED visit in six months prior to index date (ref is no)	0.2523	0.00884	-0.0345	0.0144
Number of days spent in hospital in year prior to index (continuous)	0.0217	0.000539	0.0115	0.0004
Income quintile 1 – Lowest	0.0130	0.0127	-0.0084	0.0202
Income quintile 2	0.00272	0.0125	-0.0099	0.0200
Income quintile 3	-0.00501	0.0128	0.0135	0.0205
Income quintile 4 – 4th highest (ref is highest)	-0.00456	0.0129	0.0427	0.0207
Scale	NA	NA	1.3790	0.0132

Table J. Model output – secondary analysis of hospitalization only, STOPP D8

	Logistic Regression		GLM	
	Number of observations	1,241	**Number of observations**	318
	Dependent variable	Any costs from hospitalization (Yes/No)	**Dependent variable**	Costs from hospitalizations
Model variables	**Coefficient**	**SE**	**Coefficient**	**SE**
Intercept	-4.2373	0.8119	9.8818	0.8494
Had a PIP	0.4659	0.0975	-0.5813	0.2003
Age (continuous)	0.0318	0.00892	-0.0007	0.0088
Sex female (ref male)	0.0685	0.0792	-0.0365	0.1494
ADG count (continuous)	0.0461	0.0210	-0.0211	0.0191
Did not have a MedsCheck	0.0589	0.1245	0.3930	0.2379
Number of prescribers	-0.1157	0.0346	0.0045	0.0319
Lived in an urban setting (ref rural)	-0.1949	0.1102	0.2852	0.2000
Number of unique medications at index date (continuous)	0.0525	0.0234	0.0019	0.0216
ED visit in six months prior to index date (ref is no)	0.7820	0.0971	-0.2467	0.2005
Number of days spent in hospital in year prior to index (continuous)	0.00339	0.00333	-0.0032	0.0033
Income quintile 1 – Lowest	0.0965	0.1106	0.0126	0.2021
Income quintile 2	0.1485	0.1108	-0.0853	0.2008
Income quintile 3	0.0853	0.1212	-0.0622	0.2232
Income quintile 4 – 4th highest (ref is highest)	0.0343	0.1210	0.0382	0.2220
Scale	NA	NA	0.7856	0.0537

Table K. Model output – secondary analysis of hospitalization only, STOPP J6

	Logistic Regression		GLM	
	Number of observations	10,190	**Number of observations**	218
	Dependent variable	Any costs from hospitalization (Yes/No)	**Dependent variable**	Costs from hospitalizations
Model variables	**Coefficient**	**SE**	**Coefficient**	**SE**
Intercept	-6.5202	0.9035	8.1147	0.8427
Had a PIP	0.0110	0.0796	-0.0654	0.1637
Age (continuous)	0.0260	0.0123	0.0131	0.0123
ADG count (continuous)	0.0784	0.0215	-0.0165	0.0210
Did not have a MedsCheck	-0.0266	0.1188	-0.0900	0.2365
Number of prescribers	-0.00099	0.0404	-0.0087	0.0404
Lived in an urban setting (ref rural)	0.0471	0.1030	0.1283	0.2014
Number of unique medications at index date (continuous)	0.0803	0.0278	0.0872	0.0280
ED visit in six months prior to index date (ref is no)	0.3722	0.0881	0.2832	0.1855
Number of days spent in hospital in year prior to index (continuous)	0.0522	0.00856	0.0080	0.0034
Income quintile 1 – Lowest	-0.1612	0.1234	-0.1034	0.2387
Income quintile 2	-0.0115	0.1070	-0.2484	0.2057
Income quintile 3	-0.00393	0.1051	-0.3613	0.1975
Income quintile 4 – 4th highest (ref is highest)	0.0595	0.1009	-0.4770	0.1952
Scale	NA	NA	1.1729	0.1003

Table L. Model output – secondary analysis of hospitalization only, STOPP K2

	Logistic Regression		GLM	
	Number of observations	6544	**Number of observations**	403
	Dependent variable	Any costs from hospitalization (Yes/No)	**Dependent variable**	Costs from hospitalization
Model variables	**Coefficient**	**SE**	**Coefficient**	**SE**
Intercept	-6.1081	0.5208	8.0443	0.6241
Had a PIP	0.4608	0.0847	-0.2084	0.1843
Age (continuous)	0.0274	0.00657	0.0128	0.0070
Sex female (ref male)	-0.00997	0.0643	0.0318	0.1350
ADG count (continuous)	0.0596	0.0160	0.0362	0.0176
Did not have a MedsCheck	-0.2787	0.1408	0.1939	0.3000
Number of prescribers	-0.0209	0.0287	0.0750	0.0284
Lived in an urban setting (ref rural)	0.0773	0.0909	-0.3554	0.1934
Number of unique medications at index date (continuous)	0.0408	0.0196	-0.0210	0.0201
ED visit in six months prior to index date (ref is no)	0.6552	0.0619	-0.6567	0.1305
Number of days spent in hospital in year prior to index (continuous)	0.0339	0.00366	-0.0065	0.0021
Income quintile 1 – Lowest	0.0661	0.0847	0.5337	0.1709
Income quintile 2	-0.0281	0.0900	0.1770	0.1883
Income quintile 3	-0.0551	0.0933	-0.1678	0.1875
Income quintile 4 – 4th highest (ref is highest)	-0.1527	0.0960	0.1596	0.2056
Scale	NA	NA	0.7900	0.0480

Chapter 5: General discussion and conclusions

5.1 Summary of results

As described in the introductory chapter, PIP in older adults is an important drug safety concern that is frequent in a large proportion of the older population in Ontario [1] and can lead to significant harm [2]. The overall aim of this thesis project was to address the knowledge gap that currently exists regarding the impact of PIP in Ontario, specifically the health system cost burden of all PIP combined, as well as the assessment of the incremental costs from distinct PIP to validate the use of PIP frequency and crude healthcare system costs as indicators of high-impact PIP. The end goal of each of these aims was to generate evidence related to the overall burden of PIP to highlight PIP as a potential high priority issue for healthcare decision makers to address at the health system level, as well as to help identify potential characteristics of high impact PIP that could help with priority setting when identifying which PIP to intervene on at a micro-level prior to implementing health system level interventions or if they cannot be implemented. These objectives were collectively addressed in Chapters 2 to 4 of this thesis.

Chapter 2 described the methods used in each of the two subsequent results manuscript chapters in detail. This chapter provided information on the study design, period of study, datasets used, population of interest, inclusion and exclusion criteria, exposure and outcomes of interest, as well as the statistical analyses to be conducted. This chapter also provided key details on the rationale for certain methodological approaches. Of note was the description of the method used to randomly assign a "PIP index date" for unexposed participants without a PIP using a random draw from the fitted time-to-PIP parametric survival model distributions of patients experiencing a PIP, which was to be used in Chapter 3. Another important section was a description of the pre-

determined approach to selecting the best fitting model when assessing incremental costs of distinct PIP criteria in Chapter 4.

Chapter 3 presented the results manuscript addressing the first objective of this thesis, which was to assess the overall health system cost burden following any PIP from hospitalizations, ED visits and newly prescribed medications in the 90-day period after a PIP in older persons in Ontario. Persons with PIP were identified as having an increased rate of hospitalizations, ED visits and newly prescribed medications. Via population attributable fraction methods, PIP was estimated to be responsible for a sizable portion of hospitalization, ED visit and newly prescribed medication costs, with hospitalization costs the most highly impacted and newly prescribed medications the lowest impacted. One interesting trend that emerged was that the impact of PIP on health system costs decreased with age, despite the prevalence of PIP increasing with age, indicating interventions should likely target younger seniors.

The study presented in Chapter 4 aimed to validate the use of PIP frequency and crude healthcare system costs as indicators of high-impact PIP via assessment of the incremental costs associated with distinct PIP criteria. Four specific STOPP/START criteria were identified as cases to be studied based on differing classification by crude healthcare costs (i.e. low, mid, high) and frequency (i.e. low, mid, high)**.** When the incremental costs among each of the cases were assessed, adjusted mean incremental costs tended to be higher for the PIPs with mid to high crude cost classifications, while drug costs appeared to be the most consistent source of costs that were in the same direction and magnitude as the total adjusted mean incremental costs when compared to the adjust mean incremental costs from hospitalizations and ED visits, indicating drug costs may also be a key PIP characteristic of interest. Additionally, prevalence was a larger factor in determining the size of estimated total health system costs due to PIP from all persons

experiencing a PIP combined than the magnitude of the estimated adjusted mean incremental costs for that PIP.

5.2 Significance of findings and future directions

In a broader sense, the results of this proposed thesis project have the potential to inform and drive change toward improved prescribing practices in Ontario and Canada, which has been a high priority issue for the federal government and a number of provincial governments [3], as well as a number of non-governmental organizations, including the Choosing Wisely campaign and the Canadian Deprescribing Network [4,5]. The evidence generated within Chapters 3 and 4 of this thesis provides a more in-depth understanding of the direct health system cost burden from any PIP in Ontario, as well as characterizes the costs associated with various PIP scenarios at the population-level and provides support for potential characteristics of high impact PIP which may be useful to healthcare decision-makers in selecting which PIPs should be intervened on and prioritized.

To contextualize the findings from this thesis, it is important to consider what some interventions to address PIP may look like. An ideal example of a macro, health system-level intervention would be the availability of some form of point of care access to medication information on any patient to their prescriber, and within such a portal PIP could be flagged and addressed as it is being prescribed. Unfortunately, no such system is in place currently, which means that micro-level interventions targeting patients and prescribers are more likely. Micro-level interventions could include, for example, periodic monitoring of prescribing quality and patient related outcomes, the development of feedback mechanisms for prescribers, or the development of targeted strategies for continuing medical education (e.g., a prescribing or deprescribing guideline) regarding specific PIP criteria [6]. Though often effective, there are a number of

barriers to implementing micro-level interventions, most notably how resource intensive they can be, particularly with a limited budget and person-time available to implement projects [7], resources which many important healthcare problems, and the interventions that aim to address them, vie for. As such, the results from this thesis highlight the importance for considering the implementation of macro-level interventions to address PIP, as well as to provide potentially useful information to help with priority setting micro-level interventions in the interim.

Burden of PIP

In line with the discussion above, there are always any number of new interventions addressing a broad range of healthcare issues in the Canadian healthcare system that require implementation, and it is very difficult to implement one, let alone all of them. These critical issues and interventions compete with one another for priority and it is important to be able to prioritize them based on high-quality evidence. The results presented in Chapter 3 provide such evidence and highlight the importance of addressing PIP given its estimated outsized burden on health system costs, based on the large PAFs for hospitalizations and ED visits, and provides all stakeholders aiming to improve the healthcare system in some way with evidence that can be used to help prioritize the place of PIP next to all of the other issues that need to be intervened on in Ontario and Canada. It is also important to note that Chapter 3 displays the burden from all PIP and not just some PIP. There are many different STOPP/START criteria, and the only way in which the entire burden of PIP identified in Chapter 3 can be addressed is through some macro-level interventions addressing PIP or medication appropriateness more broadly, perhaps in the form of broader policy or health informatics-based interventions that are implemented at the health system level to improve prescribing as a whole.

Characteristics of high impact PIP

As it currently stands, there are no such macro-level interventions that could address all PIP at once. While sets of PIP criteria such as the STOPP/START or Beers criteria are useful, they are costly and time consuming to apply in large numbers of people in their entirety person-by-person. As a result, should PIP be determined as a high priority area of intervention by healthcare decision-makers, they currently might be left with addressing individual, or small groups of, PIP one at a time, and the question would then turn to determining which PIP or PIPs to address first. Chapter 4 aimed to fill such a gap by attempting to validate characteristics, such as the crude healthcare costs and frequency, for use by decision makers for priority setting. The premise was that not all PIPs are equal with regards to impact, and that while some PIPs would be very costly, others may not be, so how could the higher impact PIPs be identified? We were able to identify some potential characteristics, namely the prevalence of the PIP, its crude healthcare costs and the up-front cost of the drug, which may be useful in prioritizing which PIPs to target for intervention without having to invest extensive resources into the modelling of adjusted costs for each criterion in a fashion similar to the process in Chapter 4 of this thesis. The time and money saved from having to conduct a significant number of costing studies for each PIP could be used in other research areas or put towards the development of interventions to address PIP and their implementation. It should be noted though that while some PIPs may not appear to be costly, their outcomes may be quite devastating (e.g. mortality), but such outcomes may not be captured within the cost outcomes used within the study. As such, it is important to consider both outcomes and costs when making decisions on which individual PIPs to target for intervention.

One issue to make note of is the apparent discrepancy between the impact of PIP on medication costs in Chapter 3 versus the role of the PIP medication costs in the incremental cost analyses. The likely explanation is the approaches used in each study towards the costing of PIP

medications. While the PAF from Chapter 3 for medications appears small, it represents the proportion of all medication costs, including medications not related to PIP, dispensed for the entire population over their 90-day outcome window. In Chapter 4, the only medication costs included were for that of the PIP itself.

Future research

There are many areas for future research resulting from this collection of studies. The first is further study on the health system cost burden of PIP in other jurisdictions outside of Ontario, as the studies described in Chapters 3 and 4 leveraged data only from Ontario and may not completely reflect the overall health system costs from any PIP, or the incremental costs from specific PIP, in other provinces in Canada, though we anticipate that results would be similar should these studies be replicated. A second area for future research would be to characterize the incremental costs of PIP in a larger sample of individual STOPP/START criterion, categorized by their crude costs and frequency, to confirm that the characteristics identified in Chapter 4 remain consistent and can be used for priority setting by decision makers. The third, and most important, area for future research is the development, implementation and evaluation of interventions to reduce PIP and its negative outcomes. Even relatively slight changes in practice or policy aimed at improving the quality of prescribing may lead to important reductions in health services utilization, mortality and unnecessary expenses associated with PIP.

5.3 Methodological strengths and limitations

Observational study design

In addition to the summary of results and implications of findings, it is also important to briefly discuss the potential methodological limitations, as well as the strengths, of the studies from

Chapters 3 and 4 of this thesis project, as this may help put the results into further context. Both studies in Chapters 3 and 4 leveraged observational study designs using HAD. Using linked HAD, though not originally collected for research purposes, allowed for the use of population-wide data for the vast majority of older persons in Ontario over an extended, 10-year period that would not have been possible via an RCT. Despite this advantage, observational cohort studies are ranked below RCTs in the hierarchy of evidence due to several limitations, including potential sources of bias and confounding, that limit the conclusions that may be drawn from them. Such limitations were identified and addressed as best as possible through certain methodological choices including inclusion and exclusion criteria and statistical methods.

It is important to note that even with proper adjustment for confounding and elimination of potential sources of bias, given their nature, observational studies are only evidence of association and not of causality. The strength of associations observed, as well as support from previous studies assessing the association between PIP and hospitalization, ED visits [2], and medication costs [8,9], does provide strong evidence that PIP does in fact lead to increased healthcare resource use and costs, supporting our findings. Additionally, though RCTs are considered the gold standard of evidence and are the desired study design when answering many health research questions, given that PIP is harmful, it would be unethical to randomize half of a study population to receiving a PIP. As such, an observational study is likely the only way in which to assess the impacts of PIP on patient outcomes and resulting costs.

Validity of STOPP/START criteria in HAD

Both studies presented in Chapters 3 and 4 rely on the application of a subset of the STOPP/START criteria coded for use in HAD in Ontario, Canada to ensure valid and comprehensive identification of older persons with PIP, and by extension, appropriate results and

conclusions for this thesis. At present there are no published validation studies comparing the application of the subset of the STOPP/START criteria coded for use in HAD and in a clinical setting for the same study population, though such a study is presently underway with results expected soon. This does bring into question the validity of the exposure variable used in each of the studies within this thesis, as there is the potential for low sensitivity or specificity to detect PIPs from this subset of the STOPP/START criteria applied to HAD, which would impact the identification of older persons with (and without) PIP in Chapters 3 and 4. Despite this potential limitation, the subset of STOPP/START criteria applied to obtain participant exposure in both studies of this thesis were identified conservatively to ensure that all information necessary to identify whether a PIP was present or not for each criteria was available. When considering the potential for misclassification, it is important to consider whether this bias would be differential or non-differential. In this scenario, there is no evidence that misclassification would be associated with our outcomes of interest, thus the bias is likely non-differential and biasing our measures of association towards the null. This would provide us with conservative estimates of the impact of PIP on health system costs.

Confounding

As described above, one of the major limitations that befalls all observational studies and may impact the association between exposure and outcome is the issue of confounding. The lack of randomization in observational cohort studies is one of the major potential sources of bias, as this may lead to an imbalance in confounding variables between exposed and unexposed groups. An important issue related to addressing confounding is that the results can only be as good as the data collected. Secondary use of previously collected data not intended for research purposes typically have issues related to the documentation of potential confounders, though data housed

at ICES used for this thesis is of high quality and the ability to link numerous different datasets allowed for the inclusion of many important potential confounders in all analyses. As with all observational studies, there is the potential for residual confounding to still exist within the presented studies that could impact the measures of association and predicted costs identified in Chapters 3 and 4. Despite this, we are confident that confounding by indication, which was of particular concern and likely the major source of confounding, was well accounted for by the variables included in all of our statistical models.

Approaches to costing

It is important discuss the approach taken for the costing of healthcare resource use in chapters 3 and 4, as well as the rationale for its selection. Typically, when estimating the cost-of-illness or burden of disease, there are two main approaches: 1) top-down costing and 2) bottom-up or micro-level costing [10]. For the top-down approach, the primary method is to obtain the overall expenditures for a particular cost category and to divide this by the number of events or encounters in this category to get a unit cost [11]. This type of analysis is best suited for macro-level analyses, such as general policy informing work at the population-level, and has the benefit of being less resource intensive, though may also be less specific to a particular context. In contrast, the bottom-up or micro-costing approach attaches costs (i.e. prices or the amount paid) to individual encounters and adds them up for a particular person per cost category [11]. The bottom-up approach is resource intensive, but it is setting specific, has greater specificity and is best suited for individual level analyses. In the literature, the bottom-up approach is often cited as more accurate than the top-down approach, but obtaining the necessary data is often an issue [11].

For this thesis, the bottom-up approach was available to us given access to health administrative databases with person-level costing data (i.e. units of utilization and units of costs) for all acute hospitalizations, ED visits and medications dispensed (Chapter 3 only) [10]. This overcame the most prevalent issue with the micro-costing approach, data availability, while providing us with the required flexibility to conduct our proposed statistical analyses and address the research objectives. The primary limitation with this approach in the context of this thesis is the potential for issues with data quality but given that these datasets are used for administrative purposes and health system performance monitoring at the federal and provincial levels, we anticipate such issues to be limited.

Notable statistical analyses and lessons learned

In addition to choosing the appropriate study design and adjustment for confounding, the analytical approaches taken within each of the studies was carefully selected to ensure no additional bias was introduced, as was discussed within the protocol presented in Chapter 2. Two approaches were of note.

The first approach of note was the random assignment of a "PIP index date" in participants without a PIP based on the distribution of time-to-first-PIP from patients with a similar age and sex in participants with a PIP. This approach, described in detail in Chapter 2 and leveraged in Chapter 3, was not one that was previously encountered in the literature and is an approach that could be considered for future studies in other drug safety and effectiveness research studies that are having difficulties identifying an appropriate time point for baseline covariate ascertainment look-back and outcome look-forward periods in patients not experiencing the index event of interest and serving as a control or unexposed group. This approach may be particularly useful in situations where matching is not possible or inefficient due to large numbers of exposed

participants relative to available unexposed, or in situations where assignment of an event index date using a variable may make the unexposed group systematically different from the exposed group and introduce bias. One improvement on this approach that could be used in future studies is increasing the number of iterations of random index event date assignments done, if possible. In the case of the study in Chapter 3 we were only able to conduct two additional random "PIP index date" assignments due to limitations in shared server space capacity. An approach similar to that used in probabilistic health economic analyses using thousands of random index event date assignments would provide better estimates of the impact of the random index event date assignment on study results [12].

The second analytical approach of note was the modelling approach taken to estimate incremental costs in Chapter 4. The predetermined steps in the protocol from Chapter 2 outlined an approach to selecting the best fitting model, but once it became time to execute those steps, it became apparent that the approach would need to be modified to adjust to the large proportion of zero costs observed. To address this, we chose to use two-part models, where the first part assessed the probability of any costs, and the second part modelled the predicted costs conditional on having any costs, after which the results from each model were combined for all observations. The predetermined steps to model building were useful for the second part of the two-part model, though there were issues with identifying the appropriate link function when a generalized linear model was needed (given evidence of heteroscedasticity with an ordinary least squares regression, i.e. steps 1 and 2 in our approach). Based on the literature, an alternative approach to model building for GLMs was used, one where the link function is selected based on theory, while the correct distribution of the GLM is selected using the modified Park's test [13]. This approach was taken instead of using the proc TRANSREG procedure in SAS [14], as was

suggested in the protocol, and a log link was selected given this is the most common power transformation for healthcare cost data [13].

5.4 Conclusions

This thesis addressed two objectives: 1) to identify the overall health system cost burden from any PIP in Ontario; 2) validate the use of PIP frequency and crude healthcare system costs as indicators of high-impact PIP via assessment of incremental costs of distinct PIP criterion. Through a large cohort of older persons in Ontario, PIP was identified as a common and costly issue, with PIP affecting hospitalization costs the most, followed by ED visits and newly prescribed medication costs. Interventions should likely target younger seniors, as the burden of PIP on health system costs was higher in younger populations despite lower PIP prevalence. Via this same cohort, it was established that the crude healthcare costs, as well as the cost of the drug causing the PIP and the frequency of the PIP are likely to be key characteristics to help guide decision makers identify high-impact PIPs, which may be useful for priority setting where no macro-level interventions to address all PIP exist. Further research is needed to assess the burden of PIP on healthcare systems in provinces outside of Ontario and to characterize the incremental costs on a larger subset of STOPP/START criteria to confirm the characteristics of high-impact PIP remain consistent and useful. Additionally, studies designing, implementing and evaluating both micro and macro-level interventions to address PIP should be conducted to improve medication appropriateness. Small improvements in medication appropriateness to reduce the incidence and prevalence of PIP could provide significant cost savings to the healthcare system while reducing harm and negative outcomes in patients.

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