# University of Alberta

The Impact of Restrictive Drug Coverage Policies on Pharmacoepidemiologic Methods and Health Outcomes

by

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A thesis submitted to the Faculty of Graduate Studies and Research
in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

Public Health Sciences



Spring 2012
Edmonton, Alberta

# ABSTRACT

The unintended consequences of restrictive drug coverage policies on epidemiologic research methods and population health outcomes have been understudied. The primary objective of this program of research was to study the impact of these policies on the magnitude and direction of potential bias within administrative database studies. This was achieved through three related studies: 1) an observational study that estimated the magnitude of drug exposure misclassification in administrative data across seven therapeutic classes; 2) a simulation cohort study that quantified the potential degree of bias resulting from varying amounts of exposure misclassification to antidiabetic drugs introduced by restrictive drug coverage policies; and 3) a real-world cohort study that measured the effect of exposure misclassification introduced by capturing benefit drug use only on observed associations between exposure and outcome.

We demonstrated that incomplete drug exposure information for drugs with a restrictive coverage policy is more common than previously thought. In fact, we found that on average, drugs with a restrictive coverage had a 40% absolute lower capture rate within one of the most widely used and accepted drug administrative databases, compared to drugs without coverage restrictions. Although our simulation study suggested a large degree of bias might be introduced when drug exposure is differentially misclassified according to a drug policy, results from our cohort study with real-world data demonstrated that a clinically important degree of bias was not apparent, at least for our three study drugs.

In addition to impacting research methods, restrictive drug coverage policies themselves may have unintended clinical consequences at the population-level. Therefore, a second major initiative of the research program was to examine the population-level impact of removing a specific restrictive coverage policy. The fourth study demonstrated that removal of a prior authorization policy for thiazolidinediones significantly influenced drug utilization but did not adversely impact health outcomes.

The results from our program of research highlight the importance of giving serious consideration to the impact of restrictive drug coverage policies when designing, analyzing, and interpreting a pharmacoepidemiologic study. Further, we demonstrate the usefulness of rigorous evaluation for understanding the population-level consequences of the removal of a drug policy.

# ACKNOWLEDGEMENT

Mr. Gamble receives salary support through a full-time Health Research Studentship from Alberta Innovates – Health Solutions (AIHS) and a Canada Graduate Scholarship from the Canadian Institutes of Health Research (CIHR). Dr. Eurich is a Population Health Investigator with AIHS and a New Investigator with the CIHR. Drs. Majumdar, Johnson, and McAlister are Health Scholars with AIHS. Dr. Majumdar holds the Faculties of Medicine and Dentistry and Pharmacy and Pharmaceutical Sciences Endowed Chair in Patient Health Management. Dr. Johnson holds a Canada Research Chair in Diabetes Health Outcomes. This program of research was funded in part by a CIHR Team Grant to the Alliance for Canadian Health Outcomes Research in Diabetes (ACHORD) (reference #: OTG-88588), sponsored by the CIHR Institute of Nutrition, Metabolism and Diabetes (INMD).

Parts of this material (Chapter 2) are based on data and information provided by the Canadian Institute for Health Information and IMS Health Brogan. However, the analyses, conclusions, opinions and statements expressed herein are those of the author, and not necessarily those of the Canadian Institute for Health Information or IMS Health Brogan.

Chapters 3, 4, and 5 were based in part on de-identified data provided by the Saskatchewan Ministry of Health. The interpretation and conclusions contained herein do not necessarily represent those of the Government of Saskatchewan or the Saskatchewan Ministry of Health.

Chapter 5 is based in part on data provided by Alberta Health and Wellness. The interpretation and conclusions contained herein are those of the researchers and do not necessarily represent the views of the Government of Alberta. Neither the Government of Alberta nor Alberta Health and Wellness express any opinion in relation to this study.

## TABLE OF CONTENTS


**CHAPTER 1: INTRODUCTION ..... 1**

1.1 STATEMENT OF THE PROBLEM ..... 1

1.1.1 THE USE OF ADMINISTRATIVE DATABASES IN PHARMACOEPIDEMIOLOGY ..... 1

*1.1.2 Administrative Claims Databases in Canada ..... 2*

*1.1.3 Drug Coverage Policies in Canada ..... 3*

*1.1.4 Effects of Restrictive Drug Coverage Policies on Drug Exposure Misclassification ..... 4*

*1.1.5 Effects of Restrictive Drug Coverage Policies on Drug Utilization and Health Outcomes ..... 7*

1.2 SUMMARY ..... 8

1.3 OBJECTIVES ..... 8

1.4 PROGRAM OF RESEARCH ..... 8

1.5 REFERENCES ..... 11

**CHAPTER 2: RESTRICTIVE DRUG COVERAGE POLICIES CAN INDUCE SUBSTANTIAL DRUG EXPOSURE MISCLASSIFICATION IN PHARMACOEPIDEMIOLOGIC STUDIES ..... 16**

2.1 INTRODUCTION ..... 16

2.2 METHODS ..... 17

2.3 RESULTS ..... 20

2.4 DISCUSSION ..... 22

2.5 REFERENCES ..... 31

**CHAPTER 3: QUANTIFYING THE IMPACT OF DRUG EXPOSURE MISCLASSIFICATION DUE TO RESTRICTIVE DRUG COVERAGE IN ADMINISTRATIVE DATABASES: A SIMULATION COHORT STUDY .. 34**

3.1 INTRODUCTION ..... 34

3.2 METHODS ..... 35
3.3 RESULTS ..... 38
3.4 DISCUSSION ..... 41
3.5 REFERENCES ..... 51

**CHAPTER 4: IMPACT OF EXPOSURE MISCLASSIFICATION DUE TO INCOMPLETE DRUG DATA IN OBSERVATIONAL STUDIES OF SAFETY AND EFFECTIVENESS ..... 53**

4.1 INTRODUCTION ..... 53
4.2 METHODS ..... 54
4.3 RESULTS ..... 57
4.4 DISCUSSION ..... 59
4.5 REFERENCES ..... 66

**CHAPTER 5: CHANGES IN THIAZOLIDINEDIONE USE AND OUTCOMES FOLLOWING REMOVAL OF A PRIOR AUTHORIZATION POLICY: CONTROLLED TIME-SERIES ANALYSIS ..... 69**

5.1 INTRODUCTION ..... 69
5.2 METHODS ..... 70
5.3 RESULTS ..... 74
5.4 DISCUSSION ..... 75
5.5 REFERENCES ..... 83

**CHAPTER 6: SUMMARY ..... 86**

6.1 SUMMARY OF RESEARCH ..... 86
6.2 IMPLICATIONS FOR FUTURE POLICY ..... 91
6.3 IMPLICATIONS FOR FUTURE RESEARCH ..... 93
6.4 REFERENCES ..... 95

# LIST OF TABLES

TABLE 1-1. CHARACTERISTICS OF PROVINCIAL ADMINISTRATIVE DRUG DATABASES ..... 10

TABLE 2-1. SELECT PHARMACOLOGICAL AGENTS AND THEIR BENEFIT STATUS FOR THE PROVINCES OF MANITOBA AND SASKATCHEWAN ..... 25

TABLE 2-2. AVERAGE MONTHLY RATIO OF PROVINCIAL DRUG CLAIMS TO RETAIL SALES DISPENSATIONS IN MANITOBA AND SASKATCHEWAN FOR DRUGS WITH AND WITHOUT RESTRICTIVE COVERAGE POLICIES, 2005-2008. ..... 28

TABLE 3-1. PERSON-YEARS (PY) OF FOLLOW-UP AND MORTALITY RATES WITHIN DRUG EXPOSURE GROUPS OF INTEREST FOR SIMULATION 1 (NON-FORMULARY POLICY) WITH NO MISCLASSIFICATION, AND 10%, 25%, AND 50% RANDOM MISCLASSIFICATION OF METFORMIN USERS ..... 45

TABLE 3-2. PERSON-YEARS (PY) OF FOLLOW-UP AND MORTALITY RATES WITHIN DRUG EXPOSURE GROUPS OF INTEREST FOR SIMULATION 2 (PRIOR AUTHORIZATION POLICY) WITH NO MISCLASSIFICATION, AND 10%, 25%, AND 50% RANDOM MISCLASSIFICATION OF METFORMIN USERS. INDEX DATES OF MISCLASSIFIED METFORMIN USERS ARE SHIFTED 10%, 25%, AND 50% OF AN INDIVIDUAL'S TOTAL FOLLOW-UP TIME ..... 46

TABLE 3-3. PERSON-YEARS (PY) OF FOLLOW-UP AND MORTALITY RATES WITHIN DRUG EXPOSURE GROUPS OF INTEREST FOR SIMULATION 3 (AGE-DEPENDENT COVERAGE POLICY) WITH NO MISCLASSIFICATION, AND SHIFTING OF INDEX DATE BASED ON AN INDIVIDUAL'S 66TH BIRTHDAY ..... 47

TABLE 4-1. CHARACTERISTICS OF 5759 USERS OF BENEFIT AND NON-BENEFIT THIAZOLIDINEDIONES ..... 62

TABLE 4-2. PRIMARY OUTCOME RESULTS FOR USERS OF BENEFIT AND NON-BENEFIT THIAZOLIDINEDIONES ..... 63

TABLE 4-3. EVENT RATES, HAZARD RATIOS, AND 95% CONFIDENCE INTERVALS FOR THE ASSOCIATION BETWEEN BENEFIT AND NON-BENEFIT USERS FOR VARIOUS DRUGS WITH RESTRICTIVE COVERAGE AND ALL-CAUSE HOSPITALIZATION OR ALL-CAUSE MORTALITY. ..... 64

TABLE 5-1. INTERNATIONAL CLASSIFICATION OF DISEASES CODES USED TO IDENTIFY CLINICAL OUTCOMES ..... 78

TABLE 5-2. PATIENT CHARACTERISTICS OF NEW-USERS OF ORAL DIABETES AGENTS IN ALBERTA (INTERVENTION) AND SASKATCHEWAN (CONTROL), CANADA, 2001 TO 2005. ..... 79

TABLE 5-3. CHANGES IN DRUG UTILIZATION, HEALTHCARE UTILIZATION, AND CLINICAL OUTCOMES AND POLICY-ATTRIBUTABLE EFFECT FROM BEFORE TO AFTER THE REMOVAL OF A PRIOR AUTHORIZATION POLICY ..... 80

# LIST OF FIGURES

FIGURE 2-1. AVERAGE RATIO OF PROVINCIAL TO RETAIL SALES DISPENSATIONS FROM 2005-2008 FOR DRUGS WITH AND WITHOUT RESTRICTIVE COVERAGE POLICIES OVER THERAPEUTIC CLASSES ..... 29

FIGURE 2-2. RATIO OF PROVINCIAL DRUG CLAIMS TO RETAIL SALES DISPENSATIONS FOR DRUGS WITH AND WITHOUT A RESTRICTIVE COVERAGE POLICY, 2005-2008..... 30

FIGURE 3-1. ADJUSTED HAZARD RATIOS FOR THE RELATIONSHIP BETWEEN ANTIDIABETIC USE AND ALL-CAUSE MORTALITY ACCORDING TO VARYING AMOUNTS OF METFORMIN DRUG EXPOSURE MISCLASSIFICATION BASED ON A HYPOTHETICAL NON-FORMULARY SIMULATION FOR METFORMIN USERS. ..... 48

FIGURE 3-2. ADJUSTED HAZARD RATIOS FOR THE RELATIONSHIP BETWEEN METFORMIN MONOTHERAPY AND ALL-CAUSE MORTALITY ACCORDING TO VARYING AMOUNTS OF METFORMIN DRUG EXPOSURE MISCLASSIFICATION BASED ON A HYPOTHETICAL PRIOR AUTHORIZATION SIMULATION FOR METFORMIN USERS. ..... 49

FIGURE 3-3. ADJUSTED HAZARD RATIOS FOR THE RELATIONSHIP BETWEEN COMBINATION (METFORMIN/SULFONYLUREA) THERAPY AND ALL-CAUSE MORTALITY ACCORDING TO VARYING AMOUNTS OF METFORMIN DRUG EXPOSURE MISCLASSIFICATION BASED ON A HYPOTHETICAL PRIOR AUTHORIZATION SIMULATION FOR METFORMIN USERS. ..... 50

FIGURE 4-1. HAZARD RATIO'S AND 95% CONFIDENCE INTERVALS FOR RISK OF ALL-CAUSE HOSPITALIZATION OR ALL-CAUSE DEATH IN USERS OF BENEFIT VERSUS NON-BENEFIT THIAZOLIDINEDIONES, CLOPIDOGREL, AND BETA-BLOCKERS (BISOPROLOL OR CARVEDILOL). ..... 65

FIGURE 5-1. PERCENT OF NEW USERS OF ORAL DIABETES AGENTS INITIATING THIAZOLIDINEDIONE THERAPY (PANEL A), METFORMIN THERAPY (PANEL B), SULFONYLUREA THERAPY (PANEL C), OR INSULIN THERAPY (PANEL D) WITHIN 30 DAYS IN ALBERTA AND SASKATCHEWAN, 2001-2005. ..... 81

# LIST OF ABBREVIATIONS

ACHORD – Alliance for Canadian Health Outcomes Research in Diabetes

ACEi – Angiotensin Converting Enzyme Inhibitor

ACS – Acute Coronary Syndrome

aHR – Adjusted Hazard Ratio

AIHS – Alberta Innovates – Health Solutions

ARB – Angiotensin Receptor Blocker

ATC – Anatomical Therapeutic Chemical

CI – Confidence Interval

CIHR – Canadian Institutes of Health Research

CIHI – Canadian Institute for Health Information

COX-2 – Cyclooxygenase-2

DSEN – Drug Safety and Effectiveness Network

ENCePP – European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

FDA – Food and Drug Administration

GEE – Generalized Estimating Equations

HF – Heart Failure

HMO – Health Maintenance Organization

ICD – International Classification of Diseases

NPDUIS – National Prescription Drug Utilization Information System

PAE – Policy Attributable Effect

PY – Person-Years

RCT – Randomized Controlled Trial

SD – Standard Deviation

TNF – Tumor Necrosis Factor

TZD – Thiazolidinedione

US – United States

# CHAPTER 1: INTRODUCTION

## 1.1 Statement of the Problem

### 1.1.1 The Use of Administrative Databases in Pharmacoepidemiology

Pharmacoepidemiologic studies are essential for understanding the full spectrum of risks and benefits of drugs. Although design properties of randomized controlled trials (RCTs) maximize the internal validity for measuring drug efficacy,[1] they are of limited value when assessing the long-term effectiveness and safety of medicines.[2] RCTs are often conducted in a relatively limited number of highly select patients, for limited duration. Indeed, RCTs typically follow patients only for a small fraction of the time the drug is used in clinical practice, especially for chronic diseases.[3] Observational studies are complementary to RCTs and address many of these limitations. They are especially useful for detecting rare adverse events and quantifying the long-term effects of drugs.[4,5] Like RCTs, however observational studies are not without limitations. Although observational studies often maximize external validity this often comes at the expense of internal validity. It is important to recognize, however, the major difference between RCTs and observational studies is in terms of the nature of the hypotheses tested in each design. Observational studies test hypotheses limited to *association*, while RCTs are better able to test if the association is *causal*.

There are two primary approaches to data collection used to conduct pharmacoepidemiologic studies: primary data collection from medical records, prospective clinical registries, or patients themselves, and secondary data collection from computerized health care records – most notably administrative claims databases. Canada is a rich source of administrative claims data, in part due to our universal health system, and these databases are commonly used to study drug safety and effectiveness.[6]

### 1.1.2 Administrative Claims Databases in Canada

In Canada, each province regulates the registration of all vital events that occur in the province such as births and deaths. All eligible provincial residents have a unique identifier assigned to them within a population registry (i.e., personal identification numbers) that includes their name, sex, age, marital status, immigration and emigration from the province, and vital statistics (date of birth and death). In addition, each province also captures health care utilization data that is linkable via the personal identification numbers. Individual level health care data generated from the claims for various health care services, including data on hospitalizations, physician visits, ambulatory care visits, and prescription drugs are recorded.

Not surprisingly, these provincial administrative datasets are increasingly being used in population health, public health, and health services research, particularly for the evaluation of drug safety and effectiveness in populations. Indeed, the recently formed Drug Safety and Effectiveness Network (DSEN) will rely heavily on provincial administrative data for assessment of drug safety and effectiveness in Canada.[6] It is important to note, however, that data collected from administrative plans often have inherent limitations, notably the lack of detailed clinical information (e.g., blood pressure, body mass index, laboratory values [lipids, complete blood count, serum creatinine, liver function tests, etc.]) and other important potential confounders (e.g., smoking status, functional status, quality of life, etc.) for important health outcomes. Another important limitation is the incomplete capture of drug exposure information. In fact, in part due to restrictive drug coverage policies, seven out of the ten Canadian provincial administrative databases do not capture complete drug information (Table 1-1). This issue extends beyond Canadian healthcare databases as virtually all health maintenance organizations (HMO's) in the United States, Medicaid and Medicare data, and some European health insurance databases do not fully capture drug exposure.[7,8]

### 1.1.3 Drug Coverage Policies in Canada

Although the Federal Government of Canada is responsible for the regulatory aspects of drug licensing, drugs are not considered medically necessary under the Canada Health Act, and therefore not formally required to be included in the provincial responsibilities.[9] Nonetheless, most provinces provide some level of insurance coverage for at least some portion of their residents.[10] The overall payment for drug therapy is therefore shared three ways between public health plans, private health insurers, and patients.

Public drug insurance in Canada, otherwise known as provincial pharmacare programs, is a changing landscape, with substantial variation in pharmacare design.[11] In general, all provinces provide outpatient drug coverage for social assistance recipients and seniors; some provinces have universal income-based catastrophic coverage. All provinces utilize drug formulary systems to specify which drugs are covered under their pharmacare program. Drugs listed on provincial formularies are based on evaluations of the efficacy, safety, and cost-effectiveness of drugs. Using various formulary management techniques such as restrictive coverage policies, cost-sharing rules, and pricing strategies, the formulary system serves primarily as a cost-containment technique.[12-15] Although the mechanisms of many of these strategies overlap, drug coverage broadly falls into one of two categories: 1) Benefit drugs and 2) Non-benefit drugs. Benefit drugs include drugs with full benefit status and drugs under a restrictive coverage policy that are approved. Non-benefit drugs include non-formulary drugs and drugs under a restrictive coverage policy that are not approved for insurance coverage. Thus, benefit status of a drug on a provincial pharmacare program is a second “hurdle” for a drug to gain market access, even after licensing approval at the federal level. A licensed drug that is available on the Canadian market, but is a non-benefit drug can be prescribed, but the province would not pay for this use.

Restrictive drug coverage policies are used by drug insurance plans throughout the world to help contain costs and encourage rationale drug prescribing.[12,16,17] In

Canada, restrictive drug coverage policies are common and frequently used for expensive therapies recently approved for use.[18] In fact, for brand name drugs approved in Canada between May 2004 and May 2009, over 80% were listed under a restrictive drug coverage policy by at least one public drug plan.[18] These policies require specific criteria to be met either at the patient level (e.g., patients must be intolerant or have tried the first line therapy prior to approval) or at the provider level (e.g., patients treated by a specialist may automatically be approved for coverage).

Restrictive coverage policies fall under various names including prior authorization, special authorization, exception drug status, limited-use status, and step therapy. We will refer to all of these polices as 'prior authorization' as this terms appears to be most widely adopted. Prior authorization policies are often very specific to each formulary and are commonly modified through time, as new clinical evidence emerges or prices changes, and sometimes even removed and reintroduced at a later date. Moreover, the process of approval may vary substantially across jurisdictions. For example, drugs subject to prior authorization may be processed using a traditional paper-based process, an online automation of approval, a pre-approved prescriber list, or by using provisional therapy to ensure immediate access for acute medications (e.g., clopidogrel).[19]

### 1.1.4 Effects of Restrictive Drug Coverage Policies on Drug Exposure Misclassification

Although administrative databases are generally accepted to accurately record drug exposure information,[20-23] they may systematically under capture drug exposure and consequently threaten the validity of a study.[24] Specific threats to the validity of drug exposure information within administrative claims databases include non-adherence,[25,26] co-payments,[27] number of days supplied,[28] free samples,[29] over-the-counter medications,[30] and time of exposure measurement.[31] Another source of drug exposure misclassification, which has been recognized, but not rigorously studied, is the impact of restrictive drug coverage policies.[27,32]

The presence of a restrictive drug coverage policy may introduce drug exposure misclassification and bias study estimates because administrative drug databases commonly only capture drug exposure data for benefit drugs – non-benefit drugs are systematically under captured. These restrictive drug policies have the potential to introduce drug exposure misclassification for either the entire drug exposure period (i.e., never captured in the administrative data) or for portions of their follow-up time (i.e., captured only when on formulary or approved via a prior authorization). Bias may be introduced if patients exposed to benefit drugs (i.e., information that is completely captured) are systematically different in their probability to experience outcomes compared to patients exposed to non-benefit drugs (i.e., information that is missing).

One option to avoid this problem of missing data is by restricting a study hypothesis to include only users of benefit drugs or by limiting the evaluation to periods when all drugs of interest were on benefits. This may partially avoid the introduction of bias; however, such a procedure becomes problematic when coverage policies change over time and potential confounders are non-benefit drugs. Delisting and prior authorization policies are often dynamic and thereby may create unexposed periods of follow-up time in administrative databases that are in fact truly exposed. Moreover, prior authorizations are common and it is unknown to what extent patients are exposed to such drugs prior to qualifying for coverage.

The prevalence of drug exposure misclassification in pharmacoepidemiologic studies as a consequence of restrictive drug coverage policies is unclear. Paterson and colleagues found that between 2000 and 2005, 15-20% of Ontario Seniors filled at least one prescription paid by a private insurer and that 20-23% of claims were through private insurance plans.[33] Further, drugs with restrictive coverage and new drugs were more likely to be missing from provincial claims data. In fact, twelve of the twenty most frequently claimed drugs through private insurance, including omeprazole, pantoprazole, clopidogrel, zopiclone, celecoxib, sildenafil, and vitamin D, had a restrictive coverage policy and would be substantially under captured by Ontario's provincial claim's

database. Hennessy and colleagues found that among US Medicaid data, several states appeared to missing prescription drug data; however, the reasons for missing data were unclear and not able to be investigated given limitations of the study design.[34]

Other literature suggests the extent of under capture appears to be substantial for several common drugs. For example, a study by Dormuth and colleagues evaluating a class of diabetes agents (thiazolidinediones [TZDs] – rosiglitazone and pioglitazone) estimated that if drug dispensations were only identified through the provincial government formulary reimbursement program, only 31% of TZD users would have been correctly classified as exposed.[35] Similarly, another Canadian study reported that only 70% of celecoxib dispensations were captured by the provincial administrative data for people less than 65 years of age.[36] Therefore, in the above studies, 30% to 70% of drug use would have been misclassified (i.e., incorrectly classified as non-exposed) if the administrative dataset had only captured provincial benefit drug use of the medication. Although these studies suggest that administrative databases may contain a substantial amount of incomplete drug exposure information, they were not designed to quantify the extent of missing drug exposure data. There are no studies to our knowledge that have systematically measured the magnitude of missing data or assessed the impact of this phenomenon on the validity of study results. Missing data in administrative databases is one of the potential unforeseen consequences of restrictive drug coverage polices.

This is an extremely important and timely issue as there are numerous examples in the literature where the primary drug of interest is subject to a restrictive drug policy and consequently drug exposure may be underestimated. Notable examples using Canadian, US, or European administrative datasets include recent studies evaluating TZDs and fracture risk,[37] TZDs and cardiovascular outcomes,[38] TZDs and new insulin analogues and cancer,[7,39] clopidogrel and mortality,[40] clopidogrel and proton-pump inhibitor interactions,[41] proton-pump inhibitors and pneumonia,[42] disease modifying anti-rheumatic agents and diabetes,[43] and COX-2 inhibitors and myocardial infarctions.[36] Many authors of these studies have acknowledged that exposure might have been

missed due to other insurance sources or out-of-pocket payment; however the extent of drug exposure misclassification resulting from these factors and the biased introduced into the study is unknown.

This issue is relevant for studying new drugs introduced into the market, which observational drug safety and effectiveness studies are particularly informative, because the majority of these drugs are listed under a restrictive coverage policy by provincial drug plans.[18,44] Furthermore, recent editorials in leading journals have highlighted the dearth of studies on health insurance coverage issues in pharmacoepidemiology.[45]

### 1.1.5 Effects of Restrictive Drug Coverage Policies on Drug Utilization and Health Outcomes

Policies restricting reimbursement are designed to reduce costs associated with the target drug without shifting costs to other healthcare expenditures or negatively impacting health outcomes. In general, restrictive coverage policies work by providing disincentives for prescribers and patients to use a higher priced drug and therefore substitute a lower priced drug with therapeutic equivalence.[14] Several reviews have highlighted that these policies may have several intended and unintended effects, including drug substitution, drug discontinuation, changes in prescribing quality, changes in adherence, changes in drug costs, changes in healthcare utilization and costs, and changes in health outcomes.[13,14,46-49] In general, restrictive drug coverage policies have been shown to reduce the use and costs of the target drug immediately after and up to two years after a policy is introduced.[14] Only a small number of drug classes have been examined, mostly gastrointestinal and non-steroidal anti-inflammatory drugs, in either low income or senior populations.[14] Further, the majority of studies have focused on short-term outcomes (e.g., <2 years), drug use, drug costs, and the introduction of polices; few studies have examined the removal of policies.[14]

## 1.2 Summary

Administrative databases are commonly used to conduct observational studies that evaluate drug safety and effectiveness. Within many of these databases, drug exposure misclassification may be present for drugs subject to a restrictive drug coverage policy and therefore, information or measurement bias may occur. The extent of exposure misclassification and potential for biased study results has been understudied and the current state of empirical evidence is very limited. Furthermore, the impact of these polices on drug utilization and population health outcomes are not well understood beyond a few specific drug classes. This program of research focused on measuring the impact of restrictive drug coverage policies on the magnitude and direction of potential bias within administrative database studies. Secondarily, the removal of a specific restrictive drug coverage policy on drug utilization and population health outcomes was evaluated.

## 1.3 Objectives

The objectives of this program of research were: 1) to estimate the degree of drug exposure misclassification and to estimate the association between restrictive drug coverage and drug exposure misclassification in administrative data; 2) to quantify the potential degree of bias resulting from exposure misclassification introduced by restrictive drug coverage policies using a series of simulations; 3) to measure the effect of non-benefit drug use in a real-world setting on observed associations between exposure and outcome, thereby documenting biases introduced when exposure status is misclassified from non-benefit drug use; 4) to assess at the population level the impact of the removal of a prior authorization policy for TZDs on drug utilization and clinical outcomes. These objectives were accomplished through a series of complementary studies.

## 1.4 Program of Research

A series of four papers contributed to the overall study goals. The first study (Chapter 2) estimated the amount of missing drug information (extent of exposure

misclassification) within two administrative databases across several therapeutic drug classes. This was accomplished by comparing provincial claims data, which were limited in capturing benefit drugs, to IMS Brogan data that captures population level data irrespective of benefit status at the point of sale. This study provided a population wide perspective on the association between restrictive drug coverage policies and drug exposure misclassification.

The second study (Chapter 3) evaluated the potential magnitude of bias introduced via restrictive drug coverage polices in a series of simulations. In this study, the effect of a restrictive coverage policy that resulted in varying degrees of misclassification through non-benefit drug use, were simulated based on a cohort of patients with diabetes obtained from administrative data from Saskatchewan Health. Specially, we simulated the effect of a 10%, 25%, 50% drug exposure misclassification for metformin and evaluated the bias introduced on study estimates of mortality compared to the base case where no misclassification occurred.

The third study (Chapter 4) measured the effect of non-benefit drug use on observed associations between exposure and outcome. We used a unique dataset from Saskatchewan Health that captures all drugs irrespective of their benefit status to measure the prevalence of non-benefit drug use, as well as, morbidity and mortality differences among benefit and non-benefit drug users. In addition, we documented the amount of bias that was introduced when conducting a typical observational drug safety and effectiveness of exposure vs. no exposure for three drug classes that were subject to a restrictive drug coverage policy.

The last study (Chapter 5) explores the population level impact of the removal of a restrictive drug coverage policy for a class of diabetes agents on drug utilization and clinical outcomes. For this study, we conducted a quasi-experimental interrupted time-series analysis of a TZD prior authorization policy removal in Alberta, Canada on 30 day and 1 year drug utilization, healthcare utilization and clinical outcomes.

## Table 1-1. Characteristics of Provincial Administrative Drug Databases

| Province | Drug data available from | Population covered | Captures all drug data |
|---|---|---|---|
| NL | 2007 | 65+ / other | -- |
| NS | 1975 | 65+ / other | -- |
| PE | -- | 65+ / other | -- |
| NB | 1990 | 65+ / other | -- |
| QC | 1983 | 65+ / other | -- |
| ON | 1990 | 65 and older | -- |
| MB | 1994 / 2005* | All ages | ✓ |
| SK | 1976 / 2006* | All ages | ✓ |
| AB | 1994 | 65+ / other | -- |
| BC | 1985 / 1996* | All ages | ✓ |

***** Date from which all drug dispensation irrespective of payer is available from

Source: Moride Y, Metge CJ. *Data Sources to Support Research on Real World Drug Safety and Effectiveness in Canada: An Environmental Scan and Evaluation of Existing Data Elements*: Health Canada; Feb 15 2010.

## 1.5 References

1. Friedman L, Furberg C, DeMets D. *Fundamentals of Clinical Trials*. New York: Springer; 1998.

2. Avorn J. *Powerful Medicine: The Benefits , Risks, and Costs of Prescription Drugs*. Toronto: Random House Canada Limited; 2005.

3. Strom B. When Should One Perform Pharmacoepidemiology Studies? In: Strom B, ed. *Pharmacoepidemiology*. fourth ed. Chichester: John Wiley & Sons; 2005:59-66.

4. Avorn J. In defense of pharmacoepidemiology--embracing the yin and yang of drug research. *N Engl J Med* 2007;357:2219-2221.

5. Dreyer NA, Tunis SR, Berger M, Ollendorf D, Mattox P, Gliklich R. Why observational studies should be among the tools used in comparative effectiveness research. *Health Aff (Millwood)* 2010;29:1818-1825.

6. Moride Y, Metge CJ. *Data Sources to Support Research on Real World Drug Safety and Effectiveness in Canada: An Environmental Scan and Evaluation of Existing Data Elements*: Health Canada; Feb 15 2010.

7. Hemkens L, Grouven U, Bender R, et al. Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues: a cohort study. *Diabetologia* 2009;52:1732-1744.

8. Aparasu RR, ed *Research Methods for Pharmaceutical Practice and Policy*. London, UK: Pharmaceutical Press; 2011. Pharmacy Business Administration Series.

9. Metge CJ, Sketris I. Pharmaceutical Policy. In: MacKinnon N, ed. *Safe and Effective: The Eight Essential Elements of an Optimal Medication-Use System*. Ottawa, ON: Canadian Pharmacists Association; 2007:117-158.

10. Lemmens T, Bouchard RA. Regulation of Pharmaceuticals in Canada. In: Downie J, Caulfield T, Flood C, eds. *Canadian Health Law and Policy*. third ed. Markham: LexisNexis; 2007:312-365.

11. Daw JR, Morgan SG. Stitching the gaps in the Canadian public drug coverage patchwork? A review of provincial pharmacare policy changes from 2000 to 2010. *Health Policy* 2012;104:19-26.

12. Angus D, Karpetz H. Pharmaceutical Policies in Canada: Issues and Challenges. *Pharmacoeconomics* 1998;14:81-96.

13. Morrison A, MacKinnon N, Hartnell N, McCaffrey K. Impact of drug plan management policies in Canada: A systematic review. *Can Pharm J* 2008;141:332-338.

14. Green C, Maclure M, Fortin P, Ramsay C, Aaserud M, Bardal S. Pharmaceutical policies: effects of restrictions on reimbursement. *Cochrane Database of Systematic Reviews* 2010;Issue 8:Art. No.: CD008654. DOI: 008610.001002/14651858.CD14008654.

15. Boucher BA. Formulary decisions: then and now. *Pharmacotherapy* 2010;30:35S-41S.

16. Hamel MB, Epstein AM. Prior-authorization programs for controlling drug spending. *N Engl J Med* 2004;351:2156-2158.

17. Almarsdottir AB, Traulsen JM. Rational use of medicines–an important issue in pharmaceutical policy. *Pharm World Sci* 2005;27:76-80.

18. Gamble JM, Weir DL, Johnson JA, Eurich DT. Analysis of drug coverage before and after the implementation of Canada's Common Drug Review. *CMAJ* 2011;183:E1259-1266.

19. LeLorier J, Bell A, Bougher D, Cox J, Turpie A. Drug reimbursement policies in Canada--need for improved access to critical therapies. *Ann Pharmacother* 2008;42:869-873.

20. Tamblyn R, Lavoie G, Petrella L, Monette J. The use of prescription claims databases in pharmacoepidemiological research: the accuracy and comprehensiveness of the prescription claims database in Québec. *J Clin Epidemiol* 1995;48:999-1009.

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

22. West SL, Savitz DA, Koch G, Strom BL, Guess HA, Hartzema A. Recall accuracy for prescription medications: self-report compared with database information. *Am J Epidemiol* 1995;142:1103-1112.

23. West S, Strom B, Freundlich B, Normand E, Koch G, Savitz D. Completeness of prescription recording in outpatient medical records from a health maintenance organization. *J Clin Epidemiol* 1994;47:165-171.

24. Stergachis AS. Record linkage studies for postmarketing drug surveillance: data quality and validity considerations. *Drug Intell Clin Pharm* 1988;22:157-161.

25. Tobi H, van den Heuvel NJ, de Jong-van den Berg LT. Does uncollected medication reduce the validity of pharmacy dispensing data? *Pharmacoepdiemiol Drug Saf* 2004;13:497-500.

26. Shrank WH, Choudhry NK, Fischer MA, et al. The epidemiology of prescriptions abandoned at the pharmacy. *Ann Intern Med* 2010;153:633-640.

27. West SL, Strom BL, Poole C. Validity of Pharmacoepidemiologic Drug and Diagnois Data. In: Strom BL, ed. *Pharmacoepidemiology*. fourth ed. Chichester: John Wiley & Sons; 2005:709-765.

28. McMahon A, Evans J, McGilchrist M, McDevitt D, MacDonald T. Drug exposure risk windows and unexposed comparator groups for cohort studies in pharmacoepidemiology. *Pharmacoepdiemiol Drug Saf* 1998;7:275-280.

29. Jacobus S, Schneeweiss S, Chan KA. Exposure misclassification as a result of free sample drug utilization in automated claims databases and its effect on a pharmacoepidemiology study of selective COX-2 inhibitors. *Pharmacoepdiemiol Drug Saf* 2004;13:695-702.

30. Yood M, Campbell U, Rothman K, et al. Using prescription claims data for drugs available over-the-counter (OTC). *Pharmacoepdiemiol Drug Saf* 2007;16:961-968.

31. Ray W, Thapa P, Gideon P. Misclassification of current benzodiazepine exposure by use of a single baseline measurement and its effects upon studies of injuries. *Pharmacoepdiemiol Drug Saf* 2002;11:663-669.

32. Schneeweiss S, Avorn J. A review of uses of health care utilization databases for epidemiologic research on therapeutics. *J Clin Epidemiol* 2005;58:323-337.

33. Paterson J, Suleiman A, Hux J, Bell C. How complete are drug history profiles that are based on public drug benefit claims? *Can J Pharmacol* 2008;15:e108-116.

34. Hennessy S, Bilker WB, Weber A, Strom BL. Descriptive analyses of the integrity of a US Medicaid claims database. *Pharmacoepdiemiol Drug Saf* 2003;12:103-111.

35. Dormuth C, Carney G, Carleton B, Bassett K, Wright J. Thiazolidinediones and Fractures in Men and Women. *Arch Intern Med* 2009;169:1395-1402.

36. Varas-Lorenzo C, Castellsague J, Stang M, Perez-Gutthann S, Aguado J, Rodriguez LA. The use of selective cyclooxygenase-2 inhibitors and the risk of acute myocardial infarction in Saskatchewan, Canada. *Pharmacoepdiemiol Drug Saf* 2009;18:1016-1025.

37. Habib Z, Havstad S, Wells K, Divine G, Pladevall M, Williams L. Thiazolidinedione use and the longitudinal risk of fractures in patients with type 2 diabetes mellitus. *J Clin Endocrinol Metab* 2010;95:592-600.

38. Loke YK, Kwok CS, Singh S. Comparative cardiovascular effects of thiazolidinediones: systematic review and meta-analysis of observational studies. *BMJ* 2011;342:d1309.

39. Lewis JD, Ferrara A, Peng T, et al. Risk of bladder cancer among diabetic patients treated with pioglitazone: interim report of a longitudinal cohort study. *Diabetes Care* 2011;34:916-922.

40. Jackevicius C, Tu J, Demers V, et al. Cardiovascular outcomes after a change in prescription policy for clopidogrel. *N Engl J Med* 2008;359:1802-1810.

41. Ho PM, Maddox TM, Wang L, et al. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. *JAMA* 2009;301:937-944.

42. Eom CS, Jeon CY, Lim JW, Cho EG, Park SM, Lee KS. Use of acid-suppressive drugs and risk of pneumonia: a systematic review and meta-analysis. *CMAJ* 2011;183:310-319.

43. Solomon DH, Massarotti E, Garg R, Liu J, Canning C, Schneeweiss S. Association between disease-modifying antirheumatic drugs and diabetes risk in patients with rheumatoid arthritis and psoriasis. *JAMA* 2011;305:2525-2531.

44. Gamble J, Eurich D, Johnson J. A Comparison of Drug Coverage in Alberta before and after the Introduction of the National Common Drug Reveiw Process. *Healthcare Policy* 2010;6:e117-e144.

45. Dreyer NA. Making observational studies count: shaping the future of comparative effectiveness research. *Epidemiology* 2011;22:295-297.

46. Puig-Junoy J, Moreno-Torres I. Impact of pharmaceutical prior authorisation policies : a systematic review of the literature. *Pharmacoeconomics* 2007;25:637-648.

47. Soumerai SB. Benefits and risks of increasing restrictions on access to costly drugs in Medicaid. *Health Aff (Millwood)* 2004;23:135-146.

48. Lexchin J. Effects of restrictive formularies in the ambulatory care setting. *Am J Manag Care* 2002;8:69-76.

49. MacKinnon NJ. Prior authorization programs: a critical review of the literature. *J Manag Care Pharm* 2001;7:297-302.

# CHAPTER 2: RESTRICTIVE DRUG COVERAGE POLICIES CAN INDUCE SUBSTANTIAL DRUG EXPOSURE MISCLASSIFICATION IN PHARMACOEPIDEMIOLOGIC STUDIES

## 2.1 Introduction

A fundamental underpinning of any pharmacoepidemiologic study is accurate drug exposure information. One method of obtaining individual drug exposure is through dispensation records obtained through administrative databases, with the major advantages of providing large samples or population-based estimates.[1] Administrative drug claims data is considered by many to be highly accurate, especially compared to outpatient records and patient recall.[2-6] However, administrative databases do not capture primary non-adherence,[7,8] free samples,[9] or over-the-counter medications.[10] Moreover, another source of drug exposure misclassification that has been recognized,[11,12] but not rigorously studied, are restrictive drug coverage policies.

Restrictive drug coverage policies, defined as either a non-formulary status or a policy that requires pre-specified criteria be met prior to approval for a drug (i.e., limited-use, prior or special authorization, step-therapy), may result in drug exposure misclassification because administrative drug databases only capture dispensations for reimbursed drugs. As individuals prescribed these drugs may pay for them out of pocket or through alternate drug coverage plans, these restrictive policies have the potential to result in drug exposure misclassification over all or some portion of the observation period, depending on the nature or status of the policy (e.g., a drug may change from restrictive to full coverage after a policy change or a patient passes a certain age threshold to qualify for full drug coverage). These restrictive formularies are employed in virtually every health care system in the world including provincial formularies within Canada and health maintenance organizations (HMO's) within the United States (US).

Given the frequent use of these large administrative databases for defining drug exposure in pharmacoepidemiologic studies, it is important to evaluate the potential magnitude of misclassification that may result as a consequence of restrictive drug coverage policies. Therefore, we conducted a population-based observational study to

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describe the degree of drug exposure misclassification and to estimate the association between restrictive drug coverage and drug exposure misclassification.

## 2.2 Methods

### *Study Design*

We conducted a population-based observational study comparing drug dispensation rates over four years (2005-2008) from two Canadian Provinces which have comparable comprehensive universal drug insurance programs and specifically do not have age-based drug insurance restrictions (i.e., the provincial drug formulary extends to younger and older patients). Specifically, we estimated the proportion of monthly dispensations captured by provincial claims data compared to dispensations captured by retail sales data among drugs subject to a restrictive drug coverage policy and drugs covered under formulary with no restrictions (i.e., full benefit status). Although we expected that drugs subject to a restrictive coverage policy would have a lower ratio of provincial dispensations to retail sales dispensations compared to drugs listed as a full benefit on the provincial formularies, we were uncertain of the degree of potential drug misclassification as this has never been formally evaluated. This study protocol received ethics approval from the Health Research Ethics Board at the University of Alberta.

### *Data Sources*

Provincial drug claims were obtained from The National Prescription Drug Utilization Information System (NPDUIS). NPDUIS is a pan-Canadian database administered by the Canadian Institute for Health Information (CIHI) containing drug utilization data from six provinces.[13-16] We excluded the other four provinces from this study as, unlike Manitoba and Saskatchewan, they only capture dispensations for limited groups of individuals, often only those over 65 or with low income. In addition to dispensation claims data, NPDUIS includes information related to drug benefit status, drug plans, and population statistics. Individuals covered by provincial workers

compensation boards or federal drug programs are not included in the NPDUIS database.[17,18] Only drug claims reimbursed by the provincial drug plan are included.

IMS Brogan collects data from more than 65,000 Canadian health care settings including over 5,000 pharmacies, hospitals, physicians, pharmaceutical manufacturers and wholesalers. IMS Brogan's CompuScript database collects sales data from 2/3 of all retail pharmacies in Canada and provides a projected estimate of the number of dispensations and units dispensed from Canadian Retail pharmacies. Projections are based on spatial statistical methodology assuming stores in close proximity have a similar behaviour. Information is available by province, drug class, subclass, molecule, and strength. IMS Brogan databases have been used in numerous pharmacoepidemiological studies,[19-23] and are considered to be reliable indicators of drug utilization.

***Study Drugs***

We selected a convenience sample of 75 of the top 150 prescription drugs from a broad range of seven therapeutic classes: acid-reducing drugs, analgesics, cardiovascular drugs, central nervous system drugs, diabetes drugs, osteoporosis drugs, and respiratory drugs (Table 2-1). Drugs were classified into the aforementioned mutually exclusive groups based on their World Health Organization Anatomical Therapeutic Chemical (ATC) classification. Drugs were selected based on their frequent utilization, the existence of restrictive coverage policies, and the availability of a control medication (a drug with full benefit status in both study provinces).[24,25]

***Variables of Interest***

We defined the IMS Brogan's CompuScript data as the "reference standard" for drug dispensations and our primary outcome was the ratio of average monthly dispensations from retail pharmacies (the IMS Brogan data) detected using provincial drug claims data. This ratio serves as a measure of drug exposure misclassification – the lower the ratio, the lower the ability of provincial drug claims databases to correctly capture drug exposure.

Drugs were classified as either having no coverage restrictions or as having a restrictive coverage policy based on their benefit status at the time of the claim in the NPDUIS. Drugs with restrictive coverage included drugs with limited-use policies, special or prior authorization policies, or non-formulary status. Limited-use and prior authorization policies require patients to meet pre-specified clinical criteria prior to coverage approval (e.g., treatment failure or intolerance with first line therapies). Limited-use policies are less restrictive than prior authorization policies and usually require the pharmacist to include a specific code when billing the third party payer; whereas prior authorization policies are often more laborious and may require health providers to phone, fax, or mail a detailed account of the patients clinical history. To account for policy changes throughout our study period we used a time-dependent variable for each drug. For example, rosiglitazone was subject to prior authorization in Manitoba until February 2007 after which it was given full benefit status. In this case, rosiglitazone would be classified under the restrictive coverage policy group prior to February 2007 and under the no coverage restrictions group from February 2007 onward.

***Statistical Analysis***

Linear regression was used to estimate the association between restrictive drug coverage policies and misclassification of drug exposure in provincial claims data. Our primary independent variable of interest was the presence or absence of a restrictive coverage policy. Within drug correlation due to serial measurements over time was accounted for using generalized estimating equations (GEE).[26] The GEE assumed a Gaussian distribution of the dependent variable and an autoregressive correlation structure. Although we describe our results using the ratio of provincial drug claims to retail sales dispensations, we used a natural logarithm transformation within our analysis to normalize the distribution of our dependent variable. A multivariable model was used to test the independent effect of restrictive drug coverage on drug exposure misclassification; covariates included in the model included province, therapeutic drug class, proportion of dispensations to people 65 years of age and older, and time.

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We tested for differences among provinces and therapeutic drug class by using interaction terms added to the primary statistical model. To explore the effect of the less restrictive limited-use policy compared to the more restrictive prior authorization policy, we categorized our primary independent variable of interest into three mutually exclusive groups: drugs with no coverage restrictions (reference), prior authorization drugs, and limited-use drugs. Moreover, to test the robustness of our results against assumptions made in categorizing drugs we undertook two additional sensitivity analyses. First, we excluded drugs that contributed monthly dispensation information to both the no coverage restriction group and restrictive coverage policy group due to one or more specific dosages or formulations having different coverage policies (e.g., no coverage restriction for regular release formulation but restricted coverage for extended release formulation). Second, we excluded drugs with less than 100 dispensations per month. All analyses were conducted using Stata-SE 11.0 (StataCorp LP, College Station, TX).

## 2.3 Results

We included 75 unique drugs of which 37 were not subject to any coverage restrictions (i.e., full benefit status) in both provinces, 27 were subject to a restrictive coverage policy in both provinces, 10 had a discordant coverage policy status between provinces, and 1 drug had a coverage policy change during the study. The majority of drugs studied were central nervous system drugs (n = 18) and cardiovascular drugs (n = 17), followed by respiratory drugs (n = 11), diabetes drugs (n = 10), acid-reducing drugs (n = 8), analgesics (n = 7), and osteoporosis drugs (n = 4).

On average, 84% of monthly dispensations were captured by provincial claims data compared to retail sales dispensation data between 2005 and 2008. Among drugs without a restrictive drug coverage policy, provincial claims captured 100% of IMS dispensations; however, among drugs subject to a restrictive coverage policy only 61% of actual dispensations were captured (crude risk ratio 0.61, 95% CI 0.51-0.72), with the extent of under-capture (i.e., drug misclassification) varying from 57% to 66% between

drug classes (Figure 2-1, Table 2-2). When limited-use drugs were categorized separately, 87% of dispensations were captured in the provincial drug claims datasets.

Our adjusted model (Figure 2-2) showed a consistent relationship, whereby restrictive coverage policies were associated with a 35% lower proportion of monthly dispensation capture by provincial claims data compared to retail sales data (adjusted risk ratio 0.65, 95% CI 0.56-0.75). We observed a significant difference in effect between provinces ($p < 0.01$ for interaction). Although drugs with restrictive coverage policies in Manitoba were captured at a considerably higher proportion than those in Saskatchewan (74% vs. 51%), this was due to a higher prevalence of the limited-use policy for drugs in Manitoba. When a limited-use status indicator was included in the regression model the interaction was no longer significant. No significant differences in effect were observed among therapeutic drug classes ($p > 0.1$ for all interaction terms).

Defining formulary status into three mutually exclusive categories (no coverage restrictions (reference), prior authorization drugs, and limited-use drugs) in the adjusted model, we found limited-use status was not associated with under-capture of provincial to retail sales dispensations (adjusted risk ratio 0.92, 95% CI 0.78–1.07). Consistent with our primary analysis, prior authorization status was associated with under-capture of dispensations (adjusted risk ratio 0.49, 95% CI 0.42-0.56). When we excluded drugs that had both no coverage restrictions and restrictive coverage policies in the same month due to dosage-specific or formulation-specific policies (10.8% of monthly observations) our results were consistent with our primary analysis (adjusted risk ratio 0.67, 95% CI 0.55-0.80). Similarly, when we excluded drugs with less than 100 dispensations per month (2.9% of monthly observations) we found a consistent relationship between restrictive coverage and under capture of provincial claims dispensations compared to retail sales dispensations (adjusted risk ratio 0.63, 95% CI 0.54-0.73).

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## 2.4 Discussion

Given the increasing use of restrictive coverage policies to manage drug use and expenditures in Canada and the US, our results have important implications for the interpretation of pharmacoepidemiologic studies. Specifically, our results suggest that drugs with a restrictive coverage policy are significantly and substantially under captured within administrative drug claims databases. This 40% discrepancy between full benefit and restricted status drugs in the capture rate with provincial dispensation claims compared to total retail pharmacy dispensations suggests substantial misclassification bias for drugs with restrictive coverage policies is possible in pharmacoepidemiologic studies. Further, this discrepancy was consistent in direction and magnitude across seven major therapeutic drug classes for both acute and chronic conditions.

Our approximation of the extent of potential drug exposure misclassification is consistent with others who have reported significant under capture of drug exposure when claims data limited to reimbursed provincial dispensations was used for individual agents.[24,25] For example, Dormuth et al,[25] using the population-based administrative health care databases of British Columbia, estimated that if only drug dispensations identified through the provincial government formulary reimbursement program were used, only 31% of TZD users in the province of BC would have been correctly classified as users/non-users. Furthermore, Paterson et al found that 15-20% of Ontario Seniors filled at least one prescription paid by a private insurer and that drugs subject to restrictive coverage policies and newer drugs were more likely to be missing from provincial claims data.[24] Our large comprehensive evaluation of restrictive drug coverage policies overcomes the limitations of these two previous studies (i.e., single drug and age restrictions) and suggests a substantial degree of drug exposure misclassification may be present in provincial drug claims databases for drugs with restrictive coverage policies irrespective of the patient population or drug classes. Importantly, inclusion of drugs with restrictive drug coverage policies in a pharmacoepidemiologic study either as a primary exposure of interest or as a covariate for adjustment may introduce substantial bias.

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Although the nature and significance of this misclassification bias will vary between studies, it is imperative that researchers are aware and transparent about the presence of any drug policies that could lead to this type of drug exposure misclassification within administrative drug claims databases. Importantly, the direction of bias (towards or away from the null) introduced by drug exposure misclassification will vary between studies and will depend on whether the study is examining harm or benefit. These restrictive coverage policies (including, but not limited to, non-formulary, prior authorization, step-therapy, or high co-payments) are not uncommon and utilized in Canada and in the US.[27] For example, in the province of Ontario there were over 98,000 patients that received medications under a prior authorization policy in 2005/2006.[28]

Although we were able to compare drug claim data from two Canadian provinces, which provide drug coverage for all citizens with drug retail sales data in those provinces, our study is not without limitations. First, our measure of drug exposure misclassification was based on monthly dispensation data. Therefore our study does not measure individual level drug exposures and must be interpreted at a population level. Second, the NPDUIS does not capture dispensations from federally sponsored drug plans but these dispensations will be captured at their point of sale. However, although NPDUIS would systematically under-capture dispensations within the Federal plans, this would occur for both the restrictive coverage policy and no coverage restrictions drugs; therefore our ratios would not be affected and no bias would be introduced into our results. Third, the extent to which our results can be generalized to other administrative databases that routinely capture formulary medications is unknown; however, inclusion of several therapeutic classes and two provinces with population-based drug coverage improves the generalizability of our results. Moreover, our results would be applicable to other secondary sources of data such as US commercial administrative and clinical health care databases. Systematic gaps in drug exposure information exist in many of these databases including electronic health records within integrated delivery networks as non-network services are not usually captured (i.e., a visit to a non-network specialist).[29]

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***Conclusions***

Drugs subject to restrictive coverage policies are under captured in administrative databases that are limited to data on drugs that were potentially reimbursed by the payer. This effect is substantial and consistent across several therapeutic drug classes. The resulting drug exposure misclassification due to restrictive drug coverage policies may induce substantial information bias, potentially leading to invalid results in pharmacoepidemiologic studies which evaluate outcomes with restrictive coverage medications (such as TZDs, cox-2 inhibitors, proton-pump inhibitors, TNF blockers, atypical antipsychotics, etc.). Therefore, pharmacoepidemiologists should consider the formulary status of a drug over the entire time period of their study and report this information in their studies. If substantial drug misclassification were possible as the drug(s) of interest had restrictive coverage policies during the timeframe of the study, administrative drug claims databases would not be appropriate to use and studies of such drugs would need to be done using databases that fully capture the drug(s) of interest.

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**Table 2-1. Select Pharmacological Agents and their Benefit Status for the Provinces of Manitoba and Saskatchewan, 2005-2008**

| Therapeutic Class | Drug | Benefit Status | |
|---|---|---|---|
| | | MB | SK |
| **Acid-reducing drugs** | cimetidine | Full benefit | Full Benefit |
| | esomeprazole | Restricted | Restricted |
| | famotidine | Full benefit | Full Benefit |
| | lansoprazole | Restricted | Restricted |
| | omeprazole | Restricted | Restricted |
| | pantoprazole | Restricted | Restricted |
| | rabeprazole | Restricted | Restricted |
| | ranitidine | Full benefit | Full Benefit |
| **Analgesics** | celecoxib | Restricted | Restricted |
| | codeine (extended release) | Restricted | Restricted |
| | codeine (immediate release) | Full benefit | Full Benefit |
| | diclofenac | Full benefit | Full Benefit |
| | fentanyl patches | Restricted | Restricted |
| | meloxicam | Restricted | Restricted |
| | naproxen | Full benefit | Full Benefit |
| **Cardiovascular drugs** | amlodipine | Full benefit | Full Benefit |
| | atenolol | Full benefit | Full Benefit |
| | atorvastatin | Full benefit | Full Benefit |
| | bisoprolol | Full benefit | Restricted |
| | carvedilol | Full benefit | Restricted |
| | clopidogrel | Restricted | Restricted |
| | enalapril | Full benefit | Full Benefit |
| | ezetimibe | Restricted | Full Benefit |
| | fenofibrate | Full benefit | Full Benefit |
| | fosinopril | Full benefit | Full Benefit |
| | furosemide | Full benefit | Full Benefit |
| | hydrochlorothiazide | Full benefit | Full Benefit |
| | metoprolol | Full benefit | Full Benefit |
| | nifedipine | Full benefit | Full Benefit |
| | ramipril | Full benefit | Full Benefit |
| | rosuvastatin | Full benefit | Full Benefit |
| | simvastatin | Full benefit | Full Benefit |
| **CNS drugs** | amitriptyline | Full benefit | Full Benefit |
| | carbidopa & levodopa | Full benefit | Full Benefit |
| | citalopram | Full benefit | Full Benefit |
| | donepezil | Restricted | Restricted |

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| Therapeutic Class | Drug | Benefit Status | |
|---|---|---|---|
| | | MB | SK |
| **CNS drugs cont'd** | fluoxetine | Full benefit | Full Benefit |
| | gabapentin | Full benefit | Full Benefit |
| | galantamine | Restricted | Restricted |
| | naratriptan | Restricted | Restricted |
| | olanzapine | Full benefit | Restricted |
| | paroxetine | Full benefit | Full Benefit |
| | quetiapine | Full benefit | Full Benefit |
| | rivastigmine | Restricted | Restricted |
| | rizatriptan | Restricted | Restricted |
| | sertraline | Full benefit | Full Benefit |
| | sumatriptan | Restricted | Restricted |
| | trazodone | Full benefit | Full Benefit |
| | venlafaxine | Full benefit | Full Benefit |
| | zolmitriptan | Restricted | Restricted |
| **Diabetes drugs** | acarbose | Full benefit | Full Benefit |
| | gliclazide | Full benefit | Restricted |
| | glimepiride | Full benefit | Restricted |
| | glyburide | Full benefit | Full Benefit |
| | metformin | Full benefit | Full Benefit |
| | metformin & rosiglitzone | Restricted | Restricted |
| | nateglinide | Restricted | Restricted |
| | pioglitazone | Restricted | Restricted |
| | repaglinide | Restricted | Restricted |
| | rosiglitazone | Full/Restricted | Restricted |
| **Osteoporosis drugs** | alendronate | Restricted | Restricted |
| | etidronate | Full benefit | Full Benefit |
| | raloxifene | Restricted | Restricted |
| | risedronate | Restricted | Restricted |
| **Respiratory drugs** | beclomethasone | Full benefit | Full Benefit |
| | budesonide | Full benefit | Full Benefit |
| | budesonide & formoterol | Full benefit | Restricted |
| | fluticasone & salmeterol | Full benefit | Restricted |
| | formoterol | Full benefit | Restricted |
| | ipratropium | Full benefit | Full Benefit |
| | montelukast | Restricted | Restricted |
| | salbutamol | Full benefit | Full Benefit |
| | salmeterol | Full benefit | Restricted |

| Therapeutic Class | Drug | Benefit Status | |
|---|---|---|---|
| | | MB | SK |
| **Respiratory drugs cont'd** | | | |
| | tiotropium | Restricted | Restricted |
| | zafirlukast | Restricted | Restricted |

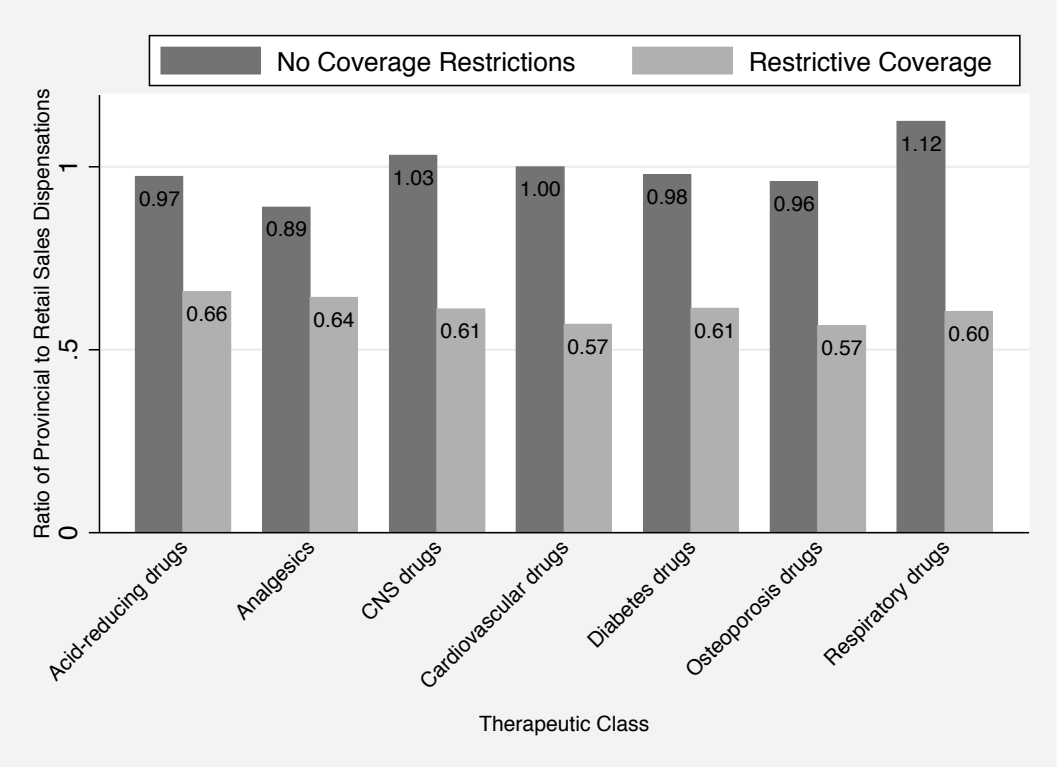
Source: National Prescription Drug Information System, CIHI

**Table 2-2. Average Monthly Ratio of Provincial Drug Claims to Retail Sales dispensations in Manitoba and Saskatchewan for Drugs With and Without Restrictive Coverage Policies, 2005-2008.**

| | Overall | Manitoba | Saskatchewan |
|---|---|---|---|
| | | mean (sd) | |
| **Overall** | | | |
| Full benefit | 1.01 (0.21) | 1.05 (0.21) | 0.96 (0.20) |
| Restricted | 0.61 (0.27) | 0.74 (0.30) | 0.51 (0.18) |
| **Acid-reducing drugs** | | | |
| Full benefit | 0.97 (0.08) | 1.01 (0.09) | 0.93 (0.05) |
| Restricted | 0.66 (0.35) | 0.78 (0.45) | 0.54 (0.10) |
| **Analgesics** | | | |
| Full benefit | 0.89 (0.13) | 0.93 (0.16) | 0.84 (0.05) |
| Restricted | 0.64 (0.27) | 0.76 (0.25) | 0.53 (0.23) |
| **Cardiovascular drugs** | | | |
| Full benefit | 1.00 (0.13) | 1.06 (0.12) | 0.93 (0.09) |
| Restricted | 0.57 (0.35) | 0.66 (0.45) | 0.51(0.23) |
| **CNS drugs** | | | |
| Full benefit | 1.03 (0.16) | 1.08 (0.20) | 0.97 (0.09) |
| Restricted | 0.61 (0.27) | 0.85 (0.16) | 0.40 (0.15) |
| **Diabetes drugs** | | | |
| Full benefit | 0.98 (0.13) | 1.07 (0.08) | 0.85 (0.06) |
| Restricted | 0.61 (0.17) | 0.60 (0.11) | 0.63 (0.22) |
| **Osteoporosis drugs** | | | |
| Full benefit | 0.96 (0.07) | 0.93 (0.08) | 0.99 (0.03) |
| Restricted | 0.57 (0.25) | 0.68 (0.25) | 0.45 (0.19) |
| **Respiratory drugs** | | | |
| Full benefit | 1.12 (0.41) | 1.08 (0.36) | 1.21 (0.48) |
| Restricted | 0.60 (0.17) | 0.71 (0.23) | 0.56 (0.10) |

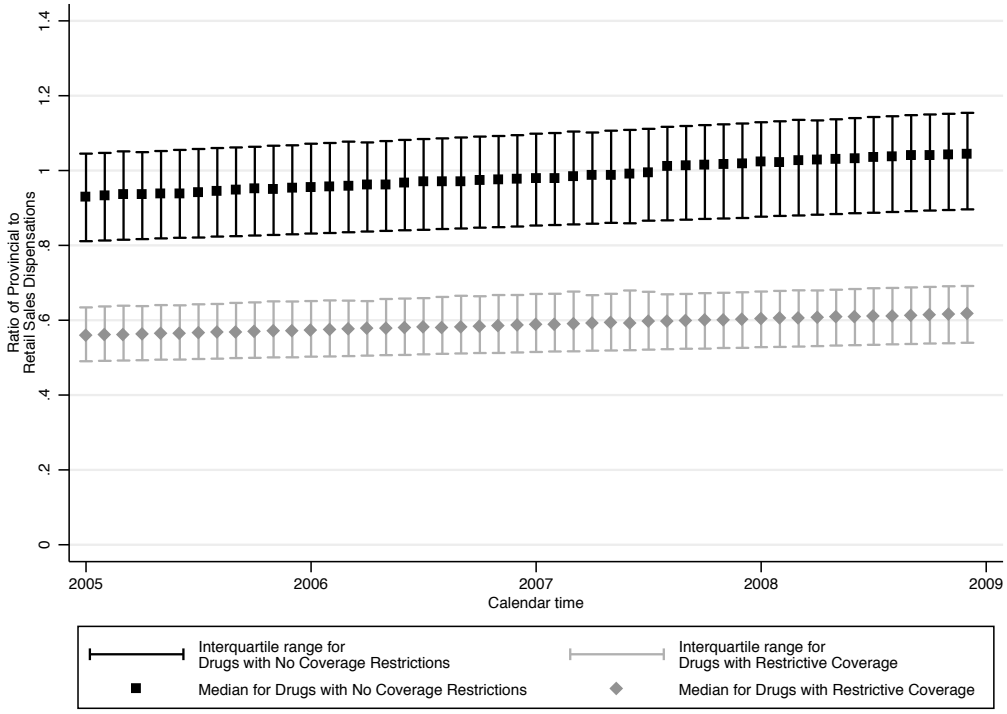
Source: CIHI, National Prescription Drug Information System; IMS Brogan, CompuScript Database

**Figure 2-1. Average Ratio of Provincial to Retail Sales Dispensations from 2005-2008 for Drugs With and Without Restrictive Coverage Policies over Therapeutic Classes**




Source: CIHI, National Prescription Drug Information System; IMS Brogan, CompuScript Database

**Figure 2-2. Ratio of Provincial Drug Claims to Retail Sales Dispensations for Drugs With and Without a Restrictive Coverage Policy, 2005-2008**




Source: CIHI, National Prescription Drug Information System; IMS Brogan, CompuScript Database

## 2.5 References

1. Weiss NS. The new world of data linkages in clinical epidemiology: are we being brave or foolhardy? *Epidemiology* 2011;22:292-294.

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

3. Tamblyn R, Lavoie G, Petrella L, Monette J. The use of prescription claims databases in pharmacoepidemiological research: the accuracy and comprehensiveness of the prescription claims database in Québec. *J Clin Epidemiol* 1995;48:999-1009.

4. West S, Strom B, Freundlich B, Normand E, Koch G, Savitz D. Completeness of prescription recording in outpatient medical records from a health maintenance organization. *J Clin Epidemiol* 1994;47:165-171.

5. West SL, Savitz DA, Koch G, Strom BL, Guess HA, Hartzema A. Recall accuracy for prescription medications: self-report compared with database information. *Am J Epidemiol* 1995;142:1103-1112.

6. West SL, Strom BL, Poole C. Validity of Pharmacoepidemiologic Drug and Diagnois Data. In: Strom BL, ed. *Pharmacoepidemiology*. fourth ed. Chichester: John Wiley & Sons; 2005:709-765.

7. Tobi H, van den Heuvel NJ, de Jong-van den Berg LT. Does uncollected medication reduce the validity of pharmacy dispensing data? *Pharmacoepdiemiol Drug Saf* 2004;13:497-500.

8. Shrank WH, Choudhry NK, Fischer MA, et al. The epidemiology of prescriptions abandoned at the pharmacy. *Ann Intern Med* 2010;153:633-640.

9. Jacobus S, Schneeweiss S, Chan KA. Exposure misclassification as a result of free sample drug utilization in automated claims databases and its effect on a pharmacoepidemiology study of selective COX-2 inhibitors. *Pharmacoepdiemiol Drug Saf* 2004;13:695-702.

A version of this chapter has been submitted for publication.

10. Yood M, Campbell U, Rothman K, et al. Using prescription claims data for drugs available over-the-counter (OTC). *Pharmacoepdiemiol Drug Saf* 2007;16:961-968.

11. Dreyer NA. Making observational studies count: shaping the future of comparative effectiveness research. *Epidemiology* 2011;22:295-297.

12. Schneeweiss S, Avorn J. A review of uses of health care utilization databases for epidemiologic research on therapeutics. *J Clin Epidemiol* 2005;58:323-337.

13. Canadian Institute for Health Information. *Antipsychotic Use in Seniors.* Ottawa Jun 17 2009.

14. Canadian Institute for Health Information. *Bisphosphonates in Osteoporosis.* Ottawa Jan 23 2009.

15. Canadian Institute for Health Information. *Drug Claims by Seniors: An Analysis Focusing on Potentially Inappropriate Medication Use, 2000-2006.* Ottawa Sep 6 2007.

16. Canadian Institute for Health Information. *Hormone Replacement Therapy: An Analysis Focusing on Drug Claims by Female Seniors, 2000-2007.* Ottawa Jun 5 2008.

17. Downey W, Stang M, Beck P, Osei W, Nichol JL. Health Services Databases in Saskatchewan. In: Strom B, ed. *Pharmacoepidemiology*. fourth ed. Chichester: John Wiley & Sons; 2005:295-310.

18. Kozyrskyj AL, Mustard CA. Validation of an electronic, population-based prescription database. *Ann Pharmacother* 1998;32:1152-1157.

19. Majumdar SR, Almasi EA, Stafford RS. Promotion and prescribing of hormone therapy after report of harm by the Women's Health Initiative. *JAMA* 2004;292:1983-1988.

20. Jackevicius CA, Tu JV, Ross JS, Ko DT, Krumholz HM. Use of ezetimibe in the United States and Canada. *N Engl J Med* 2008;358:1819-1828.

A version of this chapter has been submitted for publication.

21. Jackevicius CA, Tu JV, Ross JS, Ko DT, Carreon D, Krumholz HM. Use of fibrates in the United States and Canada. *JAMA* 2011;305:1217-1224.

22. Patten S, Williams J, Metz L. Anti-depressant use in association with interferon and glatiramer acetate treatment in multiple sclerosis. *Mult Scler* 2008;14:406-411.

23. Law M, Majumdar S, Soumerai S. Effect of illicit direct to consumer advertising on use of etanercept, mometasone, and tegaserod in Canada: controlled longitudinal study. *BMJ* 2008;337:a1055.

24. Paterson J, Suleiman A, Hux J, Bell C. How complete are drug history profiles that are based on public drug benefit claims? *Can J Pharmacol* 2008;15:e108-116.

25. Dormuth C, Carney G, Carleton B, Bassett K, Wright J. Thiazolidinediones and Fractures in Men and Women. *Arch Intern Med* 2009;169:1395-1402.

26. Hanley JA, Negassa A, Edwardes MD, Forrester JE. Statistical analysis of correlated data using generalized estimating equations: an orientation. *Am J Epidemiol* 2003;157:364-375.

27. Hamel MB, Epstein AM. Prior-authorization programs for controlling drug spending. *N Engl J Med* 2004;351:2156-2158.

28. LeLorier J, Bell A, Bougher D, Cox J, Turpie A. Drug reimbursement policies in Canada--need for improved access to critical therapies. *Ann Pharmacother* 2008;42:869-873.

29. Valuck R, Jackson B. Secondary data analysis: commercial data. In: Aparasu RR, ed. *Research Methods for Pharmaceutical Practice and Policy*. London, UK: Pharmaceutical Press; 2011:227-243.

A version of this chapter has been submitted for publication.

# CHAPTER 3: QUANTIFYING THE IMPACT OF DRUG EXPOSURE MISCLASSIFICATION DUE TO RESTRICTIVE DRUG COVERAGE IN ADMINISTRATIVE DATABASES: A SIMULATION COHORT STUDY

## 3.1 Introduction

Administrative claims databases are commonly used for pharmacoepidemiologic studies assessing the relationship between drug exposures and health outcomes.[1,2] Like any epidemiologic study, valid results from studies based on administrative claims rely on accurate classification of disease state[3] and drug exposure.[4] Misclassification bias may result in spurious conclusions of benefit or harm. Potential sources of drug exposure misclassification that are well known include non-adherence,[5] over-the-counter drug exposure,[6] and free samples.[7]

Although often overlooked, another potential source of drug exposure misclassification is restrictive drug coverage policies.[8] Administrative drug databases commonly capture drug dispensation data through an electronic claims system, whereby the only drugs captured are those that are either widely available on formulary or only covered for those patients who meet prior authorization criteria (i.e., pre-specified clinical criteria).[9] In other words, each time a pharmacist processes and dispenses a prescription specific details (e.g., drug name, dosage, quantity, price) are sent to the payer via an electronic system; however, information is only collected by the payer if the product is included in the payer's formulary. Although some administrative databases capture all drugs irrespective of drug coverage, this is the exception rather than the norm. Drug policies that limit coverage through non-formulary status or 'prior authorization' criteria for coverage are common cost-containment mechanisms employed by single party payers to guide prescribing.[10,11] However, to the extent that drugs with restrictive coverage policies are still used in the population but not captured in administrative databases, these policies have the potential to result in drug exposure misclassification in pharmacoepidemiologic studies.[8] For example, an individual's drug exposure may not be captured if they choose to pay for the medication 'out-of-pocket' or have a private (non-government) drug coverage plan.[12] This may occur over the entire drug exposure period

*A version of this chapter has been published. Gamble 2012. Value in Health;15:191-197.*

(i.e., never captured in the administrative data) or may change over time, depending on the nature of the policy (e.g., policy changed from restrictive coverage to full coverage, or a patient passes a certain age threshold and becomes eligible for coverage).

Thus, we designed this study to quantify the potential degree of bias resulting from exposure misclassification due to a policy restricting drug coverage. Specifically, we provide three simulations that represent the potential consequences of restrictive drug policies for pharmacoepidemiologic studies and measure the impact of varying degrees of both drug category misclassification and person-time exposure misclassification on estimates obtained using administrative data.

## 3.2 Methods

***Population and setting***

The data sources and population studied were previously discussed in detail.[13] Briefly, 12,272 new-users of metformin or a sulfonylurea were identified between January 1, 1991 and December 31, 1996 using the administrative databases of Saskatchewan Health. Individuals were prospectively followed to the first occurrence of death, termination of Saskatchewan Health coverage, or December 31, 1999, providing a maximum follow-up of 9 years.[13] Saskatchewan Health provides universal health coverage to its approximately one million residents with the exception of federal inmates, Royal Canadian Mounted Police, and members of the armed forces (~1% of the population). All health beneficiaries regardless of age are eligible for prescription drug coverage except those who receive these benefits through the federal government (primarily First Nations, ~9% of the population). Both metformin and glyburide were listed in the provincial formulary with unrestricted coverage for the entire study period.[14]

New users of these antidiabetic agents were categorized into mutually exclusive groups and followed from their first dispensation date (index date) of an oral antidiabetic therapy: 1626 (13%) were treated with metformin monotherapy, 4730 (39%) with sulfonylurea monotherapy, and 5916 (48%) were treated with combination of sulfonylurea

and metformin therapy. As previously reported, metformin monotherapy was associated with lower all-cause mortality compared to sulfonylurea therapy.[13] Ethical approval was obtained from the Health Ethics Research Board of the University of Alberta.

***Exposure misclassification simulations***

For the purposes of this paper, we re-analyzed the association between metformin use and all-cause mortality under varying amounts of exposure misclassification. Specifically, we conducted simulations to mimic potential consequences of three common restrictive drug policies - non-formulary status, prior authorization and age-based restrictions. We chose metformin as our 'policy drug' because there was little or no exposure misclassification of metformin in our original cohort study since it was listed as a full benefit on the formulary in Saskatchewan throughout the years of our study. Likewise, sulfonylurea use consisted almost exclusively of glyburide and was also listed as a full benefit during this period in Saskatchewan.

In our non-formulary and prior authorization simulations, we randomly selected 0% (i.e., base-case), 10%, 25%, and 50% of all metformin users to be subject to the hypothetical drug policy and therefore have their drug exposure misclassified. Random selection was conducted using a uniform random variable generator in Stata SE version 11.2 (StataCorp LP, College Station, TX) statistical software. Indeed, these simulations represent a realistic approximation of the degree of potential drug exposure misclassification- for example, a recent study reported that ~70% of thiazolidinedione users who were receiving therapy were not captured using provincial administrative data only due to a prior authorization policy resulting in the use of third party insurance or out of pocket payment for the medications.[15]

Our first policy simulation is perhaps the simplest case of a restrictive drug policy - a non-formulary drug, where exposure occurred but the administrative claims database failed to capture this via claimed dispensations. Thus, randomly selected individuals who were originally receiving metformin as monotherapy were reclassified as non-exposed and therefore removed from analyses (i.e., analysis comparing metformin vs. sulfonylurea

but would be included in a 'no use' comparison) for their entire follow-up. For metformin use in combination with sulfonylureas, individuals were reclassified as sulfonylurea monotherapy users.

Our second simulation is an example of a 'prior authorization' drug use policy, whereby an initial period of exposure may occur (e.g., through private insurance or out-or-pocket) but is not captured within the claims databases until specific coverage criteria have been met. As a result, a subject's actual or true number of person-years exposed to the policy drug would be underestimated due to the delayed capture of exposure. To simulate this 'blind period' while individuals fulfilled coverage criteria, we delayed the metformin index date for randomly selected individuals by 10%, 25%, and 50% of the total exposure time between an individual's first metformin dispensation and exit from the cohort. As in the previous simulation, we randomly selected 10%, 25%, and 50% of individuals to be subject to the hypothetical policy.

We intentionally introduced drug exposure misclassification in a random fashion for the above simulations, as there may be several reasons for why specific drugs will not be fully reimbursed. Age-based criteria, however, are often used to define eligibility criteria for drug insurance plans, of which seniors are the most common beneficiary group. We therefore, ran a third simulation whereby we considered any drug exposure prior to age 66 not available within the administrative database (even though the Saskatchewan Health datasets we used to capture prescriptions in younger patients). Drug exposure prior to age 66 was reclassified as non-exposed. Individuals who died or were censored prior to age 66 were therefore excluded from the analysis. For individuals with an oral antidiabetic index date prior to their 66$^{th}$ birthday, we shifted the index date to the date they turned 66 years of age to represent the first captured dispensation within the age based restrictive drug policy.

In summary, we varied the number of people exposed to metformin (simulation one) and the time of metformin initiation due to specific coverage (simulation two) or age based criteria (simulation three).

***Statistical analysis***

Cox proportional hazards regression models were used to assess the relationship between drug exposure and mortality. Individuals were considered exposed to metformin or sulfonylurea therapy from the date of their first dispensation until the date they died, left the province, or December 31, 1999, whichever occurred earliest. We adjusted the analyses for baseline age, sex, chronic disease score,[16] and insulin use, as previously published.[13] To estimate the adjusted hazard ratios (aHR) and confidence intervals (CI), we used 1000 bootstrap samples for the non-formulary and prior authorization simulations. For these simulations, we report the mean hazard ratio and the $2.5^{th}$ and $97.5^{th}$ percentiles of the 1000 repetitions. For the age-dependent coverage policy simulation, we report HR and 95% CI based on the eligible cohort 66 years and older. We used the HR point estimate from the base case cohort as our reference standard to assess the degree of potential bias.

## 3.3 Results

***Cohort characteristics***

We identified 12,272 new-users of oral antidiabetic agents. Mean age was 64 (SD 14) years, 55% were male, and 51% had a history of cardiovascular disease. Overall, 2681 (21.9%) individuals died over a mean follow-up period of 5.1 (SD 2.2) years. Over the entire observation period, 4730 (38.5%) individuals were exposed to sulfonylurea monotherapy, 1626 (13.3%) individuals were exposed to metformin monotherapy, and 5916 (48.2%) individuals were exposed to combination therapy (i.e., metformin and sulfonylurea).

In our base case with 0% misclassification, there were 10,286 person-years of exposure for metformin use and 32,969 person-years for sulfonylurea use. Compared to sulfonylurea monotherapy exposure, metformin monotherapy exposure was associated with a 10% absolute reduction [317 (20%) versus 1440 (30%)] and 12% relative risk reduction of mortality; adjusted hazard ratio 0.88 (95% CI 0.78-0.99)]. Tables 3-1 to 3-3

include the person-years follow-up, mortality rates, and misclassified person-years for the base case and simulation cohorts.

***Simulation one – Use of Non-Formulary Drug***

In this scenario the amount of person-time lost for the 10% to 50% misclassification of metformin monotherapy use ranged from 1017 person-years to 5211 person-years. Similarly, the apparent proportion of sulfonylurea monotherapy person-time increased from 1904 person-years to 9690 person-years (since combination users were now misclassified as sulfonylurea monotherapy users) compared to the original cohort (Table 3-1). Figure 3-1 illustrates the adjusted point estimates and their corresponding 95% confidence interval within the metformin exposure and combination exposure categories compared to sulfonylurea monotherapy for 10%, 25%, and 50% misclassification of metformin users. Compared to the full cohort without misclassification, exposure misclassifications of 10%, 25%, and 50% for metformin users overestimated the beneficial effect of metformin monotherapy compared to sulfonylurea monotherapy [i.e., decreased the relative HR] by 2% [aHR 0.86; 95% CI 0.83-0.89], 3% [aHR 0.85; 95% CI 0.79-0.89], and 6% [aHR 0.82; 95% CI 0.73-0.91]. A similar trend was observed for exposure to combination therapy compared to sulfonylurea monotherapy whereby the relative hazard estimate decreased by 3% [aHR 1.34; 95% CI 1.29-1.39], 6% [aHR 1.31; 95% CI 1.24-1.38], and 11% [aHR 1.26; 95% CI 1.16-1.36] compared to the base-case estimate (aHR 1.37,95% CI 1.26-1.50).

***Simulation two – Prior Authorization Drugs***

In simulation two, the number of individuals was identical to the base case cohort (n=12,272), however, drug exposure misclassification was induced by shifting exposure time for a random selection of individuals dispensed metformin in an attempt to mimic a prior authorization drug policy. The amount of time misclassified due to proportional shifts of person-time is shown in Table 3-2. As expected, there is more person-time misclassification as the index date for metformin therapy is shifted more dramatically. The amount of misclassified exposure time ranged from 137 person-years to 3021 person-

years for metformin and 154 person-years to 4429 person-years for sulfonylurea monotherapy.

Figures 3-2 and 3-3 depict the adjusted point estimates and 95% confidence intervals for metformin monotherapy (Figure 3-2) and combination therapy (Figure 3-3). Unlike simulation one where greater misclassification resulted in minimal changes in point estimates, the bias introduced due to delayed observation of exposure in the administrative data results in a negative shift (i.e., potentially beneficial to potentially harmful) in the point estimates for metformin therapy in all misclassification schemes. Indeed, when a random sample of 10%, 25%, and 50% of individuals exposed to metformin were selected and their index date was shifted by 50% of their metformin exposure time, the apparent benefits decreased by 7% [aHR 0.95; 95% CI 0.94-0.96], 19% [aHR 1.07; 95% CI 1.06-1.09], and 46% [aHR 1.34; 95% CI 1.31-1.38], respectively. Similar results were found when comparing combination therapy to sulfonylurea monotherapy (Figure 3-3).

***Simulation three – Age-dependent Coverage Policy***

A total of 4791 (39%) individuals were excluded in the age-dependent coverage policy simulation because they died or were censored prior to their 66$^{th}$ birthday. Of the 7481 individuals included, 3252 (43.4%) were sulfonylurea monotherapy users, 940 (12.6%) were metformin monotherapy users, and 3289 (44.0%) were combination (metformin/sulfonylurea) therapy users. The relationship between metformin monotherapy (aHR 0.89, 95% CI 0.78-1.01) compared to sulfonylurea monotherapy was consistent in magnitude and direction with the base case cohort. However, combination therapy (aHR 1.18, 95% CI 1.08-1.29) was associated with a 19% absolute lower hazard ratio compared to the base case cohort. The majority of individuals started their oral antidiabetic agents after their 66$^{th}$ birthday and therefore did not have their index date shifted. On average, an individual's index date shifted 11% of their total follow-up time. There were 1694 (22%) individuals who started an oral antidiabetic agent prior to their 66$^{th}$ birthday. For these individuals their index date was shifted 1100 (sd 724) days on

average, representing 49% of their total follow-up time. When we excluded prevalent users of metformin or a sulfonylurea between their 65th and 66th birthday, a new users analysis showed consistent results to our primary analysis for both metformin monotherapy (aHR 0.90, 95% CI 0.79-1.03) and combination therapy (aHR 1.42, 95% CI 1.29-1.56).

## 3.4 Discussion

Our analyses demonstrate that common restrictive drug coverage policies may introduce misclassification of drug exposure in administrative claims databases and thereby bias reported drug-outcome associations. Our 'non-formulary' simulation demonstrated minimal changes in the point estimate associated with our hypothetical policy drug metformin compared to sulfonylureas, suggesting an over-estimated benefit for metformin by 2-6%, depending on the proportion of metformin users affected. Our 'prior authorization' simulation, however, demonstrated an effect estimate that changed the direction of the association from one of apparent benefit to one of apparent harm. As expected, the more individuals and person-time in which drug exposure was misclassified, the larger the observed bias. Similarly, our age-dependent coverage policy simulation suggested that substantial bias could result if exposure time prior to age 65 years is ignored. When we restricted our age-dependent coverage simulation to new-users, however, risk estimates were consistent with our base case analysis.

There are several examples of restrictive drug policies that may result in a period of exposure misclassification within the administrative database, including over-the-counter medications, drug samples, prior/special authorizations, exceptional drug status, and limited use, among others. Although the extent to which over-the-counter medications and free samples induces bias is relatively limited when studying rare outcomes,[6,7] the extent to which common restrictive drug coverage policies such as prior authorization may induce bias is unknown. Our simulations provide a range of estimates for the potential magnitude of such biases. Perhaps the most important implication of our

findings is that the misclassification bias arising from a restrictive drug policy may be severe enough to potentially change the direction of a drug-outcome relationship. One option to avoid this bias is to restrict study hypotheses to include only formulary medications or to limit evaluation to periods when all drugs of interest were on formulary; this becomes problematic, however, when coverage policies change over time. Delisting and prior authorization policies are often dynamic and thereby may create apparently unexposed periods of follow-up time in administrative databases when subjects are in reality exposed.

There is little published evidence on the potential extent and direction to which 'drug policy' induces misclassification bias. In one study it was estimated that 69% of patients exposed to a thiazolidinedione would have been misclassified if the analysis were limited to only those patients with prescriptions captured in the provincial administrative database.[15] If all drugs of interest are affected equally (non-differential misclassification) by the policy the results are generally biased towards the null; however, when differential misclassification occurs (i.e., only a subset of drugs affected by policy) the direction of bias is unpredictable.[17] Moreover, the policy drug may be disproportionally affected because of factors related to both the policy and the outcome. For example, younger patients with a higher socioeconomic status are more likely to be pay 'out of pocket' or have additional private insurance and may be both less likely to experience the health outcome and be impacted by a restrictive drug coverage policy.

The method in which data is collected is central to the 'drug policy bias' that we have described and demonstrated using a real world dataset. The fact that only drugs paid for by a particular drug plan or group of plans, whether governmental or private, are included in many administrative databases is the root of the misclassification. In an effort to minimize drug exposure misclassification it is imperative that all drugs dispensed be captured. This is possible for all prescription medications as they are electronically processed and is in fact already the case for some publicly funded health care systems (e.g., British Columbia and Manitoba in Canada). Recent examples in the literature

suggest that researchers acknowledge restrictive drug coverage policies as a potential limitation in their data; however, quantification of this bias is absent. For example, Lipscombe et al. evaluated the effect of thiazolidinediones on heart failure, acute myocardial infarction, and mortality.[18] During the period of drug exposure, thiazolidinediones were only covered by the Ontario's public drug program if a physician completed a prior authorization form indicating the pre-specified coverage criteria had been met. The authors acknowledge this and report that 10-13% of coverage requests were not approved during their study period; however, it is unknown whether those denied approval were exposed to thiazolidinediones by purchasing these medications out of pocket or via private insurance or if a subset of the population who never applied for coverage were also exposed.

***Limitations***

Although we have demonstrated a potential bias present in the pharmacoepidemiology literature using real world data, our study does have limitations. First, our hypothetical drug policy example was that of a known beneficial drug evaluating only a single outcome; however, our results likely apply equally to a drug reported to have a negative effect on health outcomes or multiple endpoint studies. Second, we only evaluated a two-drug scenario. More complex drug comparisons of three or more drugs may also occur, especially in chronic diseases with multiple treatment options, and provide a greater propensity for drug exposure misclassifications within multiple exposure categories and unpredictable effects. Third, the degree of misclassification introduced within the simulations was arbitrary ranging from 10% to 50% but is likely indicative of real-world populations, as published examples illustrate.[15] Moreover, we have demonstrated that the results are highly sensitive to the degree of person-time misclassified. Fourth, our administrative data contained limited information on potential confounders, especially clinical variables (e.g., hemoglobin A1C, blood-pressure, smoking status, or lipid values); however, we selected individuals to misclassify in a random manner and therefore residual confounding is unlikely to explain our results. Last,

we used a real world cohort of individuals to represent the 'true' relationship between metformin and all-cause mortality. Although a similar protective effect of metformin has been observed in randomized controlled trials and other observational studies, our results may not be generalizable to other cohorts in which the metformin-mortality relationship is substantially different.

***Conclusions***

In conclusion, we have illustrated the potential impact of restrictive drug coverage policies creating time periods in which exposure to a particular drug (in this case metformin) may still have occurred but was not captured by an administrative drug plan database. Our results suggest that the validity of epidemiologic studies using administrative databases that evaluate drug-outcome relationships in drugs subject to restrictive coverage polices may be compromised because of drug exposure misclassification. Thus, better reporting of drug policies existent in a geographic locale during the years of study are required to fully interpret results of pharmacoepidemiology studies using administrative databases from that locale.

*A version of this chapter has been published. Gamble 2012. Value in Health;15:191-197.*

**Table 3-1. Person-years (py) of follow-up and mortality rates within drug exposure groups of interest for simulation 1 (non-formulary policy) with no misclassification, and 10%, 25%, and 50% random misclassification of metformin users**

| Variables | Drug Exposure Groups: Metformin monotherapy | Sulfonylurea monotherapy | Combination metformin/sulfonylurea therapy |
|---|---|---|---|
| **Base-Case Cohort (no misclassification of metformin users)** | | | |
| Person-years follow-up | 10,286 | 32,969 | 19,544 |
| Mortality rate per 1000py (95% CI) | 31(28-34) | 44 (42-46) | 47 (44-50) |
| Person-years misclassified | 0 | 0 | 0 |
| **10% of metformin users randomly misclassified** | | | |
| Person-years follow-up | 9,269 | 34,873 | 17,640 |
| Mortality rate per 1000py (95% CI) | 30 (27-34) | 44 (42-46) | 47 (44-50) |
| Person-years misclassified | -1,017 | 1,904 | -1,904 |
| **25% of metformin users randomly misclassified** | | | |
| Person-years follow-up | 7,683 | 37,776 | 14,737 |
| Mortality rate per 1000py (95% CI) | 32 (28-36) | 45 (43-48) | 46 (43-50) |
| Person-years misclassified | -2,603 | 4,807 | -4,807 |
| **50% of metformin users randomly misclassified** | | | |
| Person-years follow-up | 5,075 | 42,659 | 9,853 |
| Mortality rate per 1000py (95% CI) | 32 (27-37) | 45 (43-47) | 46 (41-50) |
| Person-years misclassified | -5,211 | 9,690 | -9,690 |

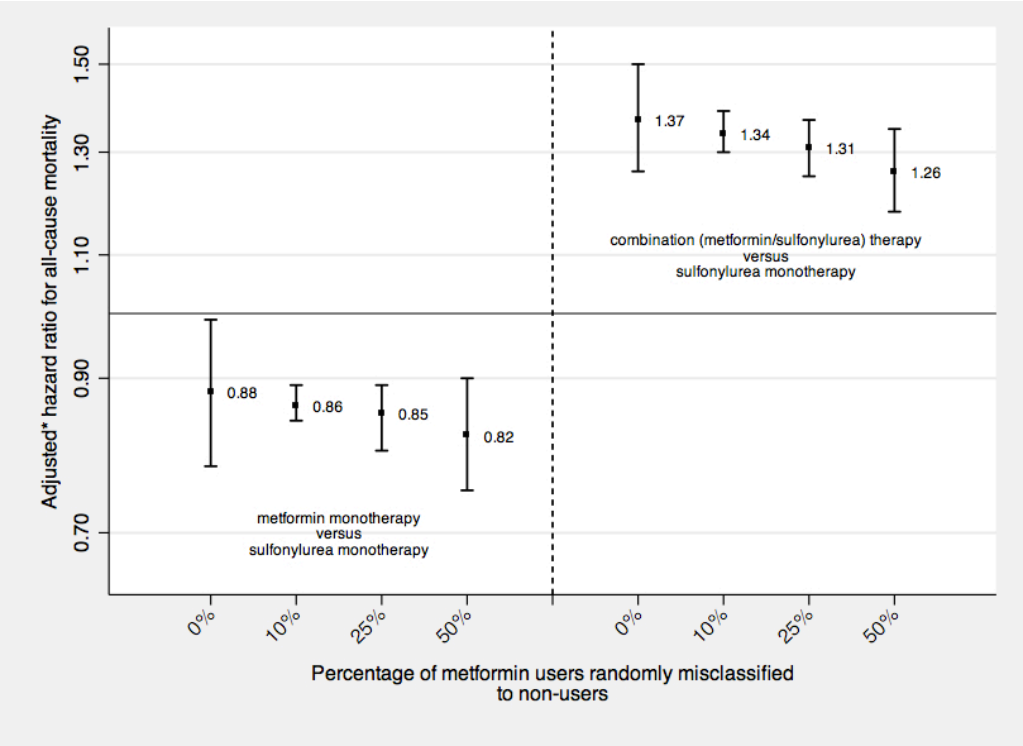
**Table 3-2. Person-years (py) of follow-up and mortality rates within drug exposure groups of interest for simulation 2 (prior authorization policy) with no misclassification, and 10%, 25%, and 50% random misclassification of metformin users. Index dates of misclassified metformin users are shifted 10%, 25%, and 50% of an individual's total follow-up time**

| | Drug Exposure Groups | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Metformin monotherapy | | | Sulfonylurea monotherapy | | | Combination metformin/sulfonylurea therapy | | |
| **Variables** | 10% index date shift | 25% index date shift | 50% index date shift | 10% index date shift | 25% index date shift | 50% index date shift | 10% index date shift | 25% index date shift | 50% index date shift |
| **Base-Case Cohort (no misclassification of metformin users)** | | | | | | | | | |
| Person-years follow-up | 10,286 | 10,286 | 10,286 | 32,969 | 32,969 | 32,969 | 19,544 | 19,544 | 19,544 |
| Mortality rate per 1000py (95% CI) | 31 (28-34) | 31 (28-34) | 31 (28-34) | 44 (42-46) | 44 (42-46) | 44 (42-46) | 47 (44-50) | 47 (44-50) | 47 (44-50) |
| Person-years misclassified | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **10% of metformin users randomly misclassified** | | | | | | | | | |
| Person-years follow-up | 10,149 | 9,960 | 9,690 | 33,123 | 33,373 | 33,833 | 19,389 | 19,140 | 18,679 |
| Mortality rate per 1000py (95% CI) | 31 (28-35) | 32 (29-36) | 33 (29-37) | 43 (41-46) | 43 (41-45) | 43 (40-45) | 48 (45-51) | 48 (45-51) | 49 (46-53) |
| Person-years misclassified | -137 | -326 | -596 | 154 | 404 | 864 | -154 | -404 | -864 |
| **25% of metformin users randomly misclassified** | | | | | | | | | |
| Person-years follow-up | 9,940 | 9,464 | 8,768 | 33,363 | 33,999 | 35,155 | 19,149 | 18,513 | 17,357 |
| Mortality rate per 1000py (95% CI) | 32 (29-36) | 33 (30-37) | 36 (33-40) | 43 (41-45) | 42 (40-45) | 41 (39-43) | 48 (45-51) | 50 (47-53) | 53 (50-57) |
| Person-years misclassified | -346 | -822 | -1,518 | 394 | 1,030 | 2,186 | -394 | -1,030 | -2,186 |
| **50% of metformin users randomly misclassified** | | | | | | | | | |
| Person-years follow-up | 9,594 | 8,651 | 7,265 | 33,767 | 35,060 | 37,398 | 18,745 | 17,453 | 15,114 |
| Mortality rate per 1000py (95% CI) | 33 (30-37) | 37 (33-41) | 44 (39-49) | 43 (40-45) | 41 (39-43) | 39 (37-41) | 49 (46-53) | 53 (50-56) | 61 (57-65) |
| Person-years misclassified | -692 | -1,635 | -3,021 | 798 | 2,091 | 4,429 | -798 | -2,091 | -4,429 |

**Table 3-3. Person-years (py) of follow-up and mortality rates within drug exposure groups of interest for simulation 3 (age-dependent coverage policy) with no misclassification, and shifting of index date based on an individual's 66th birthday**

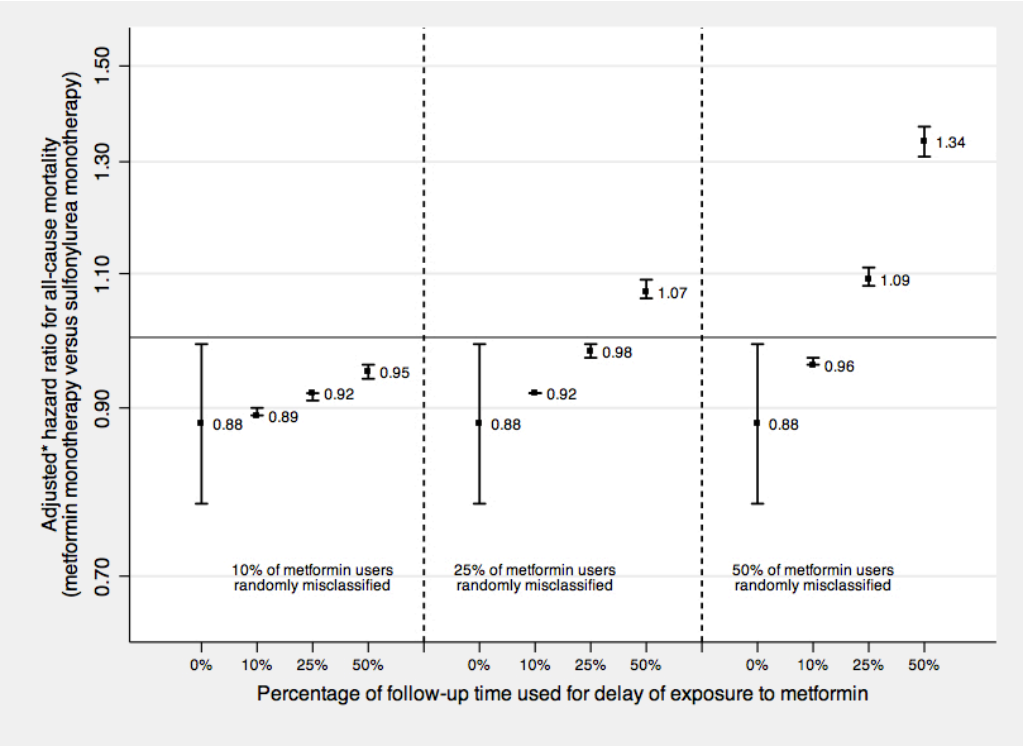
| | Drug Exposure Groups | | |
|---|---|---|---|
| **Variables** | Metformin monotherapy | Sulfonylurea monotherapy | Combination metformin/sulfonylurea therapy |
| **Base-Case Cohort (no misclassification of metformin users)** | | | |
| Person-years follow-up | 10,286 | 32,969 | 19,544 |
| Mortality rate per 1000py (95% CI) | 31(28-34) | 44 (42-46) | 47 (44-50) |
| person-years misclassified | 0 | 0 | 0 |
| **Metformin use misclassified based on age** | | | |
| Person-years follow-up | 4,821 | 18,423 | 9,307 |
| Mortality rate per 1000py (95% CI) | 54 (48-61) | 68 (64-72) | 84 (79-91) |
| person-years misclassified | -5,465 | -14,546 | -10,237 |

**Figure 3-1. Adjusted Hazard Ratios for the Relationship Between Antidiabetic Use and All-cause Mortality According to Varying Amounts of Metformin Drug Exposure Misclassification Based on a Hypothetical Non-formulary Simulation for Metformin Users.**



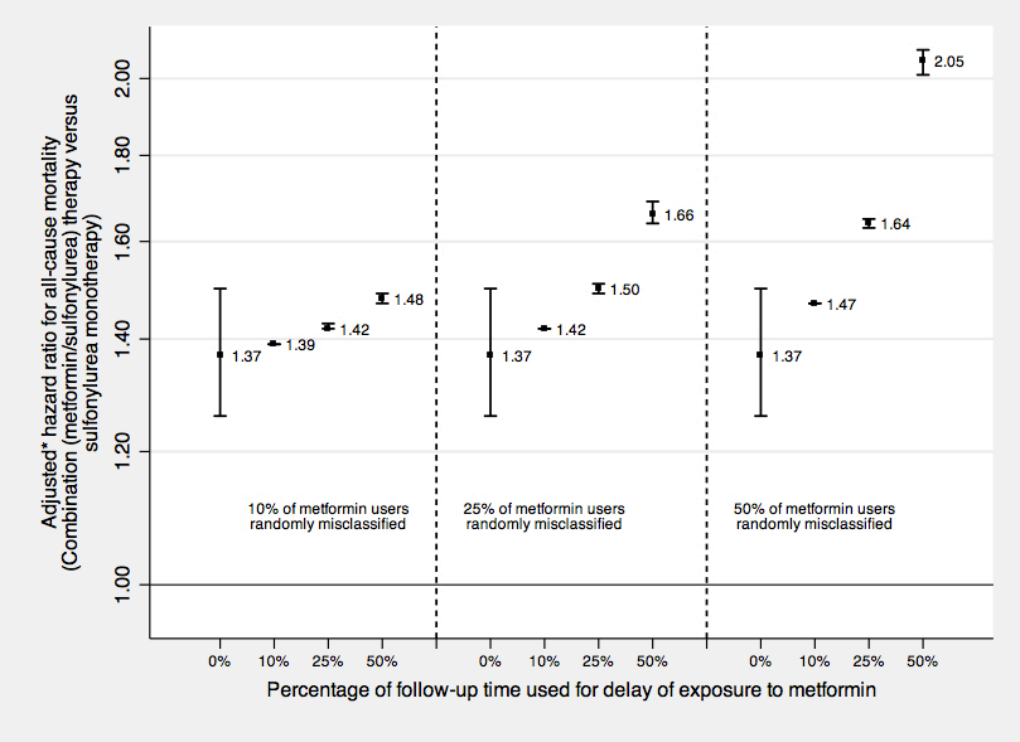

* Adjusted for age at index date, sex, chronic disease score, and insulin use.

**Figure 3-2. Adjusted Hazard Ratios for the Relationship Between Metformin Monotherapy and All-cause Mortality According to Varying Amounts of Metformin Drug Exposure Misclassification Based on a Hypothetical Prior Authorization Simulation for Metformin Users.**




* Adjusted for age at index date, sex, chronic disease score, and insulin use.

**Figure 3-3. Adjusted Hazard Ratios for the Relationship Between Combination (metformin/sulfonylurea) therapy and All-cause Mortality According to Varying Amounts of Metformin Drug Exposure Misclassification Based on a Hypothetical Prior Authorization Simulation for Metformin Users.**




* Adjusted for age at index date, sex, chronic disease score, and insulin use.

## 3.5 References

1. Ray WA. Improving automated database studies. *Epidemiology* 2011;22:302-304.

2. Rawson N, Downey W, Maxwell C, West R. 25 Years of pharmacoepidemiology innovation: the Saskatchewan Health administrative databases. *J Popul Ther Clin Pharmacol* 2011;18:e245-249.

3. Manuel D, Rosella L, Stukel T. Importance of accurately identifying disease in studies using electronic health records. *BMJ* 2010;341:c4226.

4. Stang A. Appropriate epidemiologic methods as a prerequisite for valid study results. *Eur J Epidemiol* 2008;23:761-765.

5. Van Staa T, Abenhain L, Leufkens H. A Study of the effects of exposure misclassification due to the time-window design in pharmacoepidemiologic studies. *J Clin Epidemiol* 2003;42:183-189.

6. Yood M, Campbell U, Rothman K, et al. Using prescription claims data for drugs available over-the-counter (OTC). *Pharmacoepdiemiol Drug Saf* 2007;16:961-968.

7. Jacobus S, Schneeweiss S, Chan KA. Exposure misclassification as a result of free sample drug utilization in automated claims databases and its effect on a pharmacoepidemiology study of selective COX-2 inhibitors. *Pharmacoepdiemiol Drug Saf* 2004;13:695-702.

8. Schneeweiss S, Avorn J. A review of uses of health care utilization databases for epidemiologic research on therapeutics. *J Clin Epidemiol* 2005;58:323-337.

9. Strom B. Overview of Automated Databases in Pharmacoepidemiology. In: Strom B, ed. *Pharmacoepidemiology*. fourth ed. Chichester: John Wiley & Sons; 2005:219-222.

10. Almarsdottir AB, Traulsen JM. Rational use of medicines–an important issue in pharmaceutical policy. *Pharm World Sci* 2005;27:76-80.

11. Boucher BA. Formulary decisions: then and now. *Pharmacotherapy* 2010;30:35S-41S.

*A version of this chapter has been published. Gamble 2012. Value in Health;15:191-197.*

12. Paterson J, Suleiman A, Hux J, Bell C. How complete are drug history profiles that are based on public drug benefit claims? *Can J Pharmacol* 2008;15:e108-116.

13. Johnson J, Majumdar S, Simpson S, Toth E. Decreased mortality associated with the use of metformin compared with sulfonylurea monotherapy in type 2 diabetes. *Diabetes Care* 2002;25:2244-2248.

14. Downey W, Stang M, Beck P, Osei W, Nichol JL. Health Services Databases in Saskatchewan. In: Strom B, ed. *Pharmacoepidemiology*. fourth ed. Chichester: John Wiley & Sons; 2005:295-310.

15. Dormuth C, Carney G, Carleton B, Bassett K, Wright J. Thiazolidinediones and Fractures in Men and Women. *Arch Intern Med* 2009;169:1395-1402.

16. Von Korff M, Wagner E, Saunders K. A chronic disease score from automated pharmacy data. *J Clin Epidemiol* 1992;45:197-203.

17. Rothman K, Greenland S, Lash T. Validity in Epidemiologic Studies. In: Rothman KJ, Greenland S, Lash T, eds. *Modern Epidemiology*. third ed. Philadelphia: Lippincott Williams & Wilkins; 2008:128-147.

18. Lipscombe L, Gomes T, Lévesque L, Hux J, Juurlink D, Alter D. Thiazolidinediones and cardiovascular outcomes in older patients with diabetes. *JAMA* 2007;298:2634-2643.

*A version of this chapter has been published. Gamble 2012. Value in Health;15:191-197.*

# CHAPTER 4: IMPACT OF EXPOSURE MISCLASSIFICATION DUE TO INCOMPLETE DRUG DATA IN OBSERVATIONAL STUDIES OF SAFETY AND EFFECTIVENESS

## 4.1 Introduction

Drug safety and comparative effectiveness studies often rely on secondary analysis of administrative databases.[1] However, such observational studies require accurate drug exposure data and this exposure may be misclassified within administrative databases due to non-adherence,[2] free samples,[3] and over-the-counter medication use.[4] Another source of drug exposure misclassification, which has been recognized but not rigorously studied, is the impact of a drug's benefit status within a drug insurance plan's formulary.[5-9]

Administrative databases often only capture drug exposure data for drugs which are a benefit through a government or private insurance drug plan.[10] Policies that limit or restrict drug coverage, by not listing a drug on formulary or by using a policy such as a prior authorization program, may result in drug exposure misclassification. For example, if a drug is not covered or a patient is denied coverage, a patient may pay 'out of pocket' or use an alternative drug insurance plan. Thus, the entire drug exposure period (or portions thereof) may be falsely classified as "not exposed". Moreover, drug exposure misclassification may occur if there are changes in a drug's benefit status during the study period, whereby a previously non-benefit drug may become a benefit either because the drug plan itself has changed the drug coverage policy or a patient initially denied coverage is approved later in the course of treatment. The prevalence of missing non-benefit drug use is unclear, and the impact of drug exposure misclassification on study estimates within administrative databases is unknown.

Studies within the United States (US) and Canada have indicated at least 10-20% of people may be missing drug dispensation information within certain administrative databases.[5,11] Moreover, newly marketed drugs, like NSAIDS, cardiovascular and diabetes medications were more likely to be missing from administrative claims data.[11]

A version of this chapter has been submitted for publication.

For instance, a study using Canadian administrative data indicated that up to 70% of thiazolidinedione (TZD) users would have been misclassified as 'not exposed' based on benefit records captured by the provincial drug insurance plan only.[12]

Although these studies suggest substantial misclassification of drugs and some simulation studies suggest that biased results may occur,[8] there is no empiric evidence of the impact of this misclassification on results of pharmacoepidemiologic studies. Thus, we designed this study to evaluate differences in patient characteristics and clinical outcomes comparing users of benefit and non-benefit prescriptions among several drug classes and assessed the potential magnitude of bias introduced within a typical drug safety and effectiveness study relying on benefit claims data only.

## 4.2 Methods

### *Study Design and Setting*

We conducted a population-based cohort study using the administrative health care databases of the Saskatchewan Ministry of Health.[13] There are approximately one million residents of Saskatchewan eligible for provincial health services coverage, of which 90% are eligible for prescription drug benefits. There is no age restriction for eligibility, unlike other public payer drug plans (e.g., Ontario Drug Benefits Plan or US Medicare) that are limited to patients 65 years and older.

The Saskatchewan Drug Plan operates under a variety of cost-sharing arrangements ranging from first-dollar coverage to an income-based program with some beneficiaries receiving no financial benefit from the government. Only drugs included in the Saskatchewan Formulary are eligible for coverage.

Some drugs are covered for specific patients under a prior authorization program (Exception Drug Status Program [EDS]) and quantity limits may apply to all drugs. Drugs that are not covered, herein referred to as non-benefit drugs, include drugs not listed in the provincial formulary, drugs listed in the formulary with restricted coverage and not approved under EDS, and benefit drugs exceeding quantity limits. Beginning January 1,

2006, Saskatchewan Health began capturing all prescription drugs, irrespective of benefit status, within the administrative databases at the point of sale.[14]

All dispensations for prescription drugs, regardless of payer (i.e., patient, government, or third-party insurer), are recorded either within the Saskatchewan benefit or non-benefit prescription drug database, which are mutually exclusive databases (i.e., no single prescription can be in both databases).

We obtained de-identified benefit and non-benefit drug use records from the Saskatchewan Ministry of Health, along with other health services information (population and vital statistics data, hospital separation data, and physicians claims data). Our study focused on evaluating the impact of a restrictive drug coverage policy for TZDs as a case in point, whereby coverage under Saskatchewan's EDS policy is granted only if a patient had previously failed to achieve adequate glucose control or were intolerant to metformin and sulfonylurea therapy. TZDs were chosen as there has been extensive clinical controversy regarding their use, and they have been subject to numerous observational studies, and many of these studies were conducted in large administrative databases where restrictive coverage policies were in existence that restricted TZD use but were not adjusted for by the investigators.[15,16] To assess the generalizability of our findings to other drugs subject to restrictive drug coverage polices, we evaluated clopidogrel and two beta-blockers (bisoprolol and carvedilol), as they have also been subject to a number of observational studies[17-20] and were also listed in the Saskatchewan Formulary with restricted coverage during the study period and subject to approval under the EDS program. The University of Alberta health research ethics board approved conduct of this study.

***Study Cohort and Exposure Definitions***

We studied a cohort of 34,209 new users of oral antidiabetic agents, and identified all TZD users between January 1, 2006 and December 31, 2006 using benefit and non-benefit data. Patients entered the new user cohort between 1995 and 2005

upon dispensation of their first oral antidiabetic agent and were followed until December 31, 2008, death, or disenrollment.

TZD users were grouped into two mutually exclusive categories based on the benefit status of their first TZD dispensation in 2006 (index date): 1) individuals who were receiving TZDs and met the provincial drug plan's formulary and coverage conditions (benefit TZD use); and 2) individuals who were receiving TZDs but were ineligible for benefit (non-benefit TZD use). The latter individuals were identified by at least one TZD dispensation in the non-benefit data but not the benefit data.

***Statistical Analysis***

The primary outcome for all analyses was a composite endpoint of all-cause hospitalization or all-cause mortality. Time to hospitalization or death among users of benefit and non-benefit TZDs was evaluated using Cox proportional hazards regression models (referent group was users of non-benefit TZD) adjusted for demographics (age and sex), health care utilization (defined as total physician visits, hospitalizations, and prescription drug utilization [metformin, sulfonylurea, insulin, antithrombotics (warfarin, heparin, low-molecular weight heparins, clopidogrel), angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blocking agents (ARBs), statins, diuretics, beta-blockers, calcium channel blockers (CCBs), nitrates (short and long-acting), gastric-acid suppressants (proton-pump inhibitors, histamine-2 blockers, misoprostol, sucralfate), bisphosphonates, and estrogen therapy] within the year prior to the index date and comorbidity burden using a modified version (missing codes for liver disease, dementia, hemiplegia, and HIV) of the Charlson index based on hospital and outpatient ICD-9 and ICD-10-CA codes in the year prior to an individual's first TZD dispensation in 2006.[21,22] All first order interaction terms were considered and none achieved statistical significance ($p>0.1$). There were no violations of the proportional hazard assumptions.

In addition to comparing users of benefit and non-benefit TZDs, we assessed the potential magnitude of bias that would be introduced in a study evaluating the association

between drug exposure and our composite endpoint. First, TZD exposure was restricted to only subjects receiving TZDs identified within the benefit database (i.e., typical administrative data records); this would be the typical approach whereby drug exposure is misclassified because all non-benefit drug exposure would be considered "not exposed". Second, TZD exposure was defined as all TZD users identified within the benefit and non-benefit databases (i.e., all those who were truly exposed to TZDs). The magnitude of bias was assessed by 500 bootstrapped samples of the differences in hazard ratios between TZD users vs. non-users using the two analyses previously described.[23]

***Sensitivity Analyses***

First, we examined both components of our primary composite outcome separately. Second, we restricted analyses to subjects 65 years of age and older as many administrative databases are limited to this age group. Third, all analyses were replicated with two other drug groups of interest (clopidogrel and beta-blockers subject to EDS [carvedilol and bisoprolol]). Analyses were conducted using Stata/SE version 11 (StataCorp LP, College Station, Texas).

## 4.3 Results

We identified 5759 individuals that filled at least one prescription for a TZD in 2006. Nearly 1/3 of all TZD users (1591 [28%]) received at least one non-benefit prescription and would be misclassified as "not exposed" in a typical administrative database analysis using benefit only records of the first payer. On average, users of benefit TZDs were 62 (SD 12) years of age, 57% were male, and were followed for a median of 2.7 years. Compared to users of non-benefit TZDs, users of benefit TZDs were older (mean 63 years vs. 60 years); more likely to be female (46% vs. 35%); had more comorbidities and physician visits; and had a higher use of drugs prior to cohort entry (Table 4-1).

There were 1789 (31%) subjects hospitalized and 421 (7%) died during follow-up. A total of 420 (26%) hospitalizations or deaths occurred in non-benefit TZD users compared to 1515 (36%) hospitalizations or deaths among benefit TZD users (p<0.001; Table 4-2). In adjusted analyses the risk of hospitalization or death for benefit TZD users was greater than for non-benefit TZD users: adjusted hazard ratio [aHR] 1.13, 95% 1.01-1.26).

When we examined the risk of death or hospitalization according to TZD exposure as classified by benefit use alone, TZD use was not associated with an increased risk of the combined endpoint (1515 [36%] vs. 7759 [34%]; aHR 1.04, 95% CI 0.98 – 1.10) (Figure 4-1). After correctly classifying all TZD exposure (benefit plus non-benefit use), analyses still produced similar results (1935 [34%] vs. 7339 [34%]; aHR 0.99, 95% CI 0.94 – 1.04). The bootstrapped mean difference in adjusted HR between analyses restricted to benefit TZD users compared to all users was only +0.05 [95% bootstrapped CI 0.02 - 0.08]).

**Sensitivity Analyses**

First, the relationship between benefit use and the components of our primary composite outcome were consistent (Table 4-2) whereby benefit TZD use was consistently associated with an increased risk of mortality (aHR 1.07, 95% CI 0.84 – 1.38) and hospitalization (aHR 1.12, 95% CI 1.00 – 1.26). Similarly, our analyses comparing estimates of risk with misclassified TZD vs. correctly classified TZD exposure yielded similar results for mortality (aHR 0.97, 95% CI 0.86 – 1.09 vs. aHR 0.94, 95% CI 0.85 – 1.05 for correct exposure; bootstrapped difference a non-significant +0.02, 95% CI -0.04 – 0.08) and hospitalization (aHR 1.04, 95% 0.98 – 1.11 vs. aHR 0.99, 95% CI 0.94 – 1.05 for correct exposure; bootstrapped difference +0.05, 95% CI 0.02 – 0.09).

Second, sub-group analysis for those 65 years of age of older demonstrated that benefit TZD users were not at an increased risk of hospitalization or death compared to non-benefit TZD users (aHR 1.09, 95% CI 0.93 -1.28). Analyses comparing TZD users to

non-users in those 65 years of age and older was similar to the main results (aHR 1.07, 95% CI 1.00 – 1.15 when TZD exposure restricted to benefit TZD users and aHR 1.05, 95% CI 0.98 – 1.12 for all TZD users, bootstrapped difference 0.02, 95% CI -0.02 – 0.06).

Third, we observed a 24% (372/1551) and 42% (148/351) prevalence of non-benefit use of clopidogrel and the beta-blockers (carvedilol and bisoprolol), respectively. Replication of our primary analyses using these agents was broadly consistent with analyses of TZD use (Table 4-3 and Figure 4-1). Bootstrapped differences were 0.01, 95% -0.04-0.06 for clopidogrel and 0.06, 95% CI -0.09-0.20 for the beta-blockers.

## 4.4 Discussion

The prevalence of non-benefit drug use for three classes of drugs, each with a restrictive coverage policy, ranged from 24% to 42% in our cohort of new antidiabetic drug users. Our study suggests that although misclassification of users of non-benefit drugs within administrative data as “not exposed” may slightly shift the risk estimates in studies, the difference is not likely clinically important, at least for the three different drug classes we examined. However, even when all potential measured confounders were included, benefit TZD users remained at a slightly higher risk of all-cause hospitalization or death compared to non-benefit TZD users, suggesting residual confounding according to drug coverage status.

Importantly, despite the outcome differences observed between benefit and non-benefit TZD users, our results suggest that the impact on comparative effectiveness studies limited to benefit drug users is negligible, both statistically and clinically, at least for common events such as hospitalization or mortality. Specifically, results of our bootstrap analyses suggest that analyses based on traditional administrative datasets that are restricted to benefit drug claims would have slightly biased results in comparative effectiveness studies of TZDs (5% shift in risk toward harm). The limited impact on risk of hospitalization and death is likely due to the fact that differences between benefit and non-benefit drug use in the known risk factors for these outcomes were controlled for in

adjusted analysis.

Although we did not find a significant influence on our outcome estimates despite 1/4 or more of patients being misclassified, this may not be the case as the amount of misclassification increases for a more prevalent drug. For example, a previous simulation study suggested that bias is introduced when the amount of misclassification increases above 25% for a drug to which over 60% of the cohort was exposed.[8] There are not many examples where more than half of a population is exposed to a single drug. We observed a 28%, 24%, and 42% prevalence of the use of non-benefit TZDs, clopidogrel, and the beta-blockers, respectively; this translates to a population prevalence in our cohort of approximately 30,000 diabetic subjects that is relatively low (21% for TZDs, 6% for clopidogrel, and 1% for beta-blockers).

Despite its strengths our study has several limitations. *First*, similar to other administrative claims databases, we are limited in our ability to adjust for disease severity, primarily due to the lack of clinical information available (e.g., functional status, laboratory values). *Second*, our measure of drug exposure is based on dispensations and not actual consumption. *Third*, we examined only patients with diabetes, whose baseline risk may have been sufficiently large that misclassification would not affect outcomes. *Last*, we evaluated only a select number of drugs listed with restricted coverage among a cohort of oral antidiabetic users and examined only all cause hospitalization and mortality. Whether these results hold true for other classes of medications and other types of events or within different patient populations is not known but clearly merits further study.

Our findings suggest that although selection bias is present in pharmacoepidemiologic studies restricted to benefit drug data only, the impact on study estimates is probably not clinically important and at times not even statistically significant. As the cost and complexity of drug therapies continue to escalate, it is likely that restrictive formulary systems will become increasingly implemented and the issues we raised will become more common. At the very least, it is important that researchers

acknowledge the existence of this potential bias when conducting studies of drug safety and effectiveness and determine better methods to deal with this bias. In addition, researchers should consider quantitative sensitivity analyses to try and define the potential magnitude of bias on a case-by-case basis.

A version of this chapter has been submitted for publication.

## Table 4-1. Characteristics of 5759 Users of Benefit and Non-benefit Thiazolidinediones

| Variables | Non-benefit TZD Users (n=1591) | Benefit TZD Users (n=4168) | P-value |
|---|---|---|---|
| Mean (sd) age* | 60 (12) | 63 (12) | *<0.001* |
| Age over 65, n (%) | 495 (31) | 1850 (44) | *<0.001* |
| **Sex, n (%)** | | | |
| Male | 1037 (65) | 2259 (54) | *<0.001* |
| Female | 554 (35) | 1909 (46) | *<0.001* |
| **Comorbidities†, n (%)** | | | |
| Myocardial Infarction | 20 (1) | 100 (2) | *0.007* |
| Heart Failure | 7 (0) | 66 (2) | *0.001* |
| Cerebrovascular disease | 36 (2) | 155 (4) | *0.006* |
| Hypertension | 702 (44) | 2049 (49) | *0.001* |
| Dysrhythmia | 83 (5) | 305 (7) | *0.004* |
| Angina | 184 (12) | 584 (14) | *0.015* |
| Renal disease | 30 (2) | 157 (4) | *<0.001* |
| Retinopathy | 98 (6) | 298 (7) | *0.184* |
| Cancer | 399 (25) | 1205 (29) | *0.004* |
| Mental Illness | 217 (14) | 710 (17) | *0.002* |
| **Health Care Utilization†, n (%)** | | | |
| ≥1 Hospitalizations | 1342 (84) | 3389 (81) | *0.007* |
| >12 Physician visits | 731 (46) | 2198 (53) | *<0.001* |
| **Comorbidity Scores** | | | |
| Mean (sd) Charlson score† | 0.3 (0.8) | 0.5 (1.1) | *0.017* |
| Median (IQR) chronic disease score‡ | 4 (4) | 5 (5) | *<0.001* |
| Median (IQR) number of unique drugs† | 9 (5) | 11 (6) | *<0.001* |
| **Drug Utilization†** | | | |
| Metformin | 1528 (96) | 4041 (97) | *0.083* |
| Sulfonylurea | 924 (58) | 2822 (68) | *<0.001* |
| Insulin | 119 (7) | 436 (10) | *0.041* |
| Antithrombotic | 278 (17) | 1228 (29) | *<0.001* |
| Beta-blocker | 422 (27) | 1438 (35) | *<0.001* |
| Ace-I | 1064 (67) | 3128 (75) | *0.001* |
| ARB | 482 (30) | 1440 (35) | *0.002* |
| Statin | 897 (56) | 2528 (61) | *0.003* |
| CCB | 431 (27) | 1536 (37) | *<0.001* |
| Diuretic | 819 (51) | 2671 (64) | *<0.001* |
| Nitrate | 244 (15) | 913 (22) | *<0.001* |
| Ulcer | 617 (39) | 2084 (50) | *<0.001* |
| Bisphosphonate | 50 (3) | 262 (6) | *<0.001* |
| Estrogen therapy | 124 (8) | 493 (12) | *<0.001* |

* At time of first TZD dispensation date in 2006

† In the year prior to first TZD dispensation date in 2006

‡ In the year prior to the first oral anti-diabetic dispensation

Ace-I: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; CCB: Calcium channel blocker

A version of this chapter has been submitted for publication.

## Table 4-2. Primary Outcome Results for Users of Benefit and Non-benefit Thiazolidinediones

| Outcome | Non-benefit TZD Users (n=1591) | Benefit TZD Users (n=4168) |
|---|---|---|
| **Composite** | | |
| Number of Events | 420 | 1515 |
| Event Rate* | 119 | 187 |
| HR** (95% CI) | 1 (ref) | 1.46 (1.31-1.63) |
| aHR† (95% CI) | 1 (ref) | 1.13 (1.01-1.26) |
| **Mortality** | | |
| Number of Events | 82 | 339 |
| Event Rate* | 19 | 31 |
| HR** (95% CI) | 1 (ref) | 1.64 (1.29-2.09) |
| aHR† (95% CI) | 1 (ref) | 1.07 (0.84-1.38) |
| **Hospitalization** | | |
| Number of Events | 392 | 1397 |
| Event Rate* | 112 | 173 |
| HR** (95% CI) | 1 (ref) | 1.43 (1.28-1.60) |
| aHR† (95% CI) | 1 (ref) | 1.12 (1.00-1.26) |

* per 1000 person-years; ** Crude Hazard Ratio; † Adjusted Hazard Ratio; Covariates included in the adjusted model were age when dispensed initial antidiabetic agent; sex; number of hospitalizations, physician visits, and unique drugs dispensed in the year prior to TZD index or January 1, 2006 for non-users; dummy variables for the use of metformin, sulfonylurea, insulin, anticoagulants, ACEi's, ARBs, statins, diuretics, beta-blockers, calcium channel blockers, nitrates, gastric-acid suppressants, bisphosphonates, and estrogen therapy, in the year prior to TZD index or January 1, 2006 for non-users; Charlson summary scores were used to adjust for comorbidities.

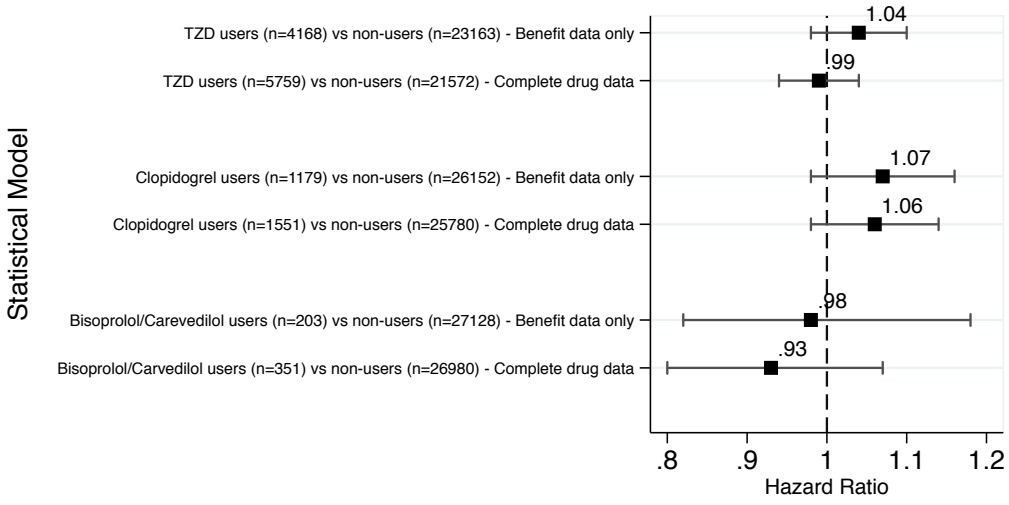
**Table 4-3. Event rates, Hazard ratios, and 95% Confidence Intervals for the Association Between Benefit and Non-benefit Users For Various Drugs with Restrictive Coverage and All-cause Hospitalization or All-cause Mortality.**

| Comparison | Number of Subjects | Number of Events | Person-Years Follow-up* | Event Rate* | HR** (95% CI) | aHR† (95% CI) |
|---|---|---|---|---|---|---|
| **TZD users** | | | | | | |
| Non-benefit | 1591 | 420 | 3506 | 119 | 1.00 (ref) | 1.00 (ref) |
| Benefit | 4168 | 1515 | 8082 | 187 | 1.46 (1.31-1.63) | 1.13 (1.01-1.26) |
| **Rosiglitazone users** | | | | | | |
| Non-benefit | 1123 | 314 | 2449 | 128 | 1.00 (ref) | 1.00 (ref) |
| Benefit | 3185 | 1159 | 6201 | 187 | 1.36 (1.20-1.54) | 1.06 (0.93-1.21) |
| **Pioglitazone users** | | | | | | |
| Non-benefit | 557 | 139 | 1244 | 112 | 1.00 (ref) | 1.00 (ref) |
| Benefit | 1656 | 566 | 3290 | 172 | 1.48 (1.20-1.74) | 1.17 (0.97-1.42) |
| **Clopidogrel users** | | | | | | |
| Non-Benefit | 372 | 171 | 640 | 267 | 1.00 (ref) | 1.00 (ref) |
| Benefit | 1179 | 642 | 1842 | 349 | 1.25 (1.06-1.48) | 1.13 (0.95-1.35) |
| **EDS Beta-blocker users‡** | | | | | | |
| Non-Benefit | 148 | 73 | 242 | 302 | 1.00 (ref) | 1.00 (ref) |
| Benefit | 203 | 126 | 281 | 448 | 1.40 (1.05-1.88) | 1.15 (0.85-1.56) |
| **Bisoprolol users** | | | | | | |
| Non-Benefit | 60 | 24 | 109 | 221 | 1.00 (ref) | 1.00 (ref) |
| Benefit | 28 | 20 | 33 | 606 | 2.21 (1.22-4.01) | 1.26 (0.57-2.78) |
| **Carvedilol users** | | | | | | |
| Non-Benefit | 88 | 49 | 133 | 368 | 1.00 (ref) | 1.00 (ref) |
| Benefit | 176 | 107 | 248 | 431 | 1.17 (0.83-1.64) | 1.06 (0.74-1.53) |

* per 1000 person-years; ** Crude Hazard Ratio; † Adjusted Hazard Ratio; Covariates included in the adjusted model were age when dispensed initial antidiabetic agent; sex; number of hospitalizations, physician visits, and unique drugs dispensed in the year prior to TZD index or January 1, 2006 for non-users; dummy variables for the use of metformin, sulfonylurea, insulin, anticoagulants, ACEi's, ARBs, statins, diuretics, beta-blockers, calcium channel blockers, nitrates, gastric-acid suppressants, bisphosphonates, and estrogen therapy, in the year prior to TZD index or January 1, 2006 for non-users; Charlson summary scores were used to adjust for comorbidities. ‡ Only includes comparisons of bisoprolol and carvedilol benefit vs. non-benefit users.

A version of this chapter has been submitted for publication.

**Figure 4-1. Hazard Ratio's and 95% Confidence Intervals for Risk of All-cause Hospitalization or All-cause Death in Users of Benefit Versus Non-benefit Thiazolidinediones, Clopidogrel, and Beta-blockers (Bisoprolol or Carvedilol).**




All models are adjusted for age when dispensed initial antidiabetic agent; sex; number of hospitalizations, physician visits, and unique drugs dispensed in the year prior to an individual's first TZD dispensation in 2006 or January 1, 2006 for non-users; dummy variables for the use of metformin, sulfonylurea, insulin, anticoagulants, ACEi's, ARBs, statins, diuretics, beta-blockers, calcium channel blockers, nitrates, gastric-acid suppressants, bisphosphonates, and estrogen therapy, in the year prior to an individual's first TZD dispensation in 2006 or January 1, 2006 for non-users; Charlson summary scores were used to adjust for comorbidities. Comparisons of bisoprolol and carvedilol do not include other beta-blockers.

## 4.5 References

1. Schneeweiss S. Developments in post-marketing comparative effectiveness research. *Clin Pharmacol Ther* 2007;82:143-156.

2. Shrank WH, Choudhry NK, Fischer MA, et al. The epidemiology of prescriptions abandoned at the pharmacy. *Ann Intern Med* 2010;153:633-640.

3. Jacobus S, Schneeweiss S, Chan KA. Exposure misclassification as a result of free sample drug utilization in automated claims databases and its effect on a pharmacoepidemiology study of selective COX-2 inhibitors. *Pharmacoepdiemiol Drug Saf* 2004;13:695-702.

4. Yood M, Campbell U, Rothman K, et al. Using prescription claims data for drugs available over-the-counter (OTC). *Pharmacoepdiemiol Drug Saf* 2007;16:961-968.

5. West SL, Strom BL, Poole C. Validity of Pharmacoepidemiologic Drug and Diagnois Data. In: Strom BL, ed. *Pharmacoepidemiology*. fourth ed. Chichester: John Wiley & Sons; 2005:709-765.

6. Schneeweiss S, Avorn J. A review of uses of health care utilization databases for epidemiologic research on therapeutics. *J Clin Epidemiol* 2005;58:323-337.

7. Dreyer NA. Making observational studies count: shaping the future of comparative effectiveness research. *Epidemiology* 2011;22:295-297.

8. Gamble J, McAlister F, Johnson J, Eurich D. Quantifying the Impact of Drug Exposure Misclassification Due to Restrictive Drug Coverage in Administrative Databases: A Simulation Study. *Value in Health* 2011;online October 19, 2011.

9. Gamble J, McAlister F, Johnson J, Eurich D. Misclassifying Drug Exposure Data within Administrative Databases: An Ecologic Approach. *Pharmacoepdiemiol Drug Saf* 2011;20:S255.

10. Strom B. Overview of Automated Databases in Pharmacoepidemiology. In: Strom B, ed. *Pharmacoepidemiology*. fourth ed. Chichester: John Wiley & Sons; 2005:219-222.

A version of this chapter has been submitted for publication.

11. Paterson J, Suleiman A, Hux J, Bell C. How complete are drug history profiles that are based on public drug benefit claims? *Can J Pharmacol* 2008;15:e108-116.

12. Dormuth C, Carney G, Carleton B, Bassett K, Wright J. Thiazolidinediones and Fractures in Men and Women. *Arch Intern Med* 2009;169:1395-1402.

13. Downey W, Stang M, Beck P, Osei W, Nichol JL. Health Services Databases in Saskatchewan. In: Strom B, ed. *Pharmacoepidemiology*. fourth ed. Chichester: John Wiley & Sons; 2005:295-310.

14. Rawson N, Downey W, Maxwell C, West R. 25 Years of pharmacoepidemiology innovation: the Saskatchewan Health administrative databases. *J Popul Ther Clin Pharmacol* 2011;18:e245-249.

15. Lipscombe L, Gomes T, Lévesque L, Hux J, Juurlink D, Alter D. Thiazolidinediones and cardiovascular outcomes in older patients with diabetes. *JAMA* 2007;298:2634-2643.

16. Habib Z, Havstad S, Wells K, Divine G, Pladevall M, Williams L. Thiazolidinedione use and the longitudinal risk of fractures in patients with type 2 diabetes mellitus. *J Clin Endocrinol Metab* 2010;95:592-600.

17. Ernst FR, Johnston S, Curkendall S, Mozaffari E, Stemkowski S. Effect of early clopidogrel discontinuation on rehospitalization in acute coronary syndrome: results from two distinct patient populations. *Am J Health Syst Pharm* 2011;68:1015-1024.

18. Ortolani P, Marino M, Marzocchi A, De Palma R, Branzi A. One-year clinical outcome in patients with acute coronary syndrome treated with concomitant use of clopidogrel and proton pump inhibitors: results from a regional cohort study. *J Cardiovasc Med* 2011;online Jan. 22, 2011.

19. Go AS, Yang J, Gurwitz JH, Hsu J, Lane K, Platt R. Comparative effectiveness of different beta-adrenergic antagonists on mortality among adults with heart failure in clinical practice. *Arch Intern Med* 2008;168:2415-2421.

A version of this chapter has been submitted for publication.

20. Kramer JM, Curtis LH, Dupree CS, et al. Comparative effectiveness of beta-blockers in elderly patients with heart failure. *Arch Intern Med* 2008;168:2422-2428; discussion 2428-2432.

21. Quan H, Bing Li L, Saunders L, et al. Assessing Validity of ICD-9-CM and ICD-10 Administrative Data in Recording Clinical Conditions in a Unique Dually Coded Database. *Health Serv Res* 2008;43:1424-1441.

22. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 2005;43:1130-1139.

23. Vittinghoff E, Glidden D, Shiboski S, McCulloch C. *Regression Methods in Biostatistics: Linear, Logistic, Survival, and Repeated Measures Models*. New York: Springer; 2005.

A version of this chapter has been submitted for publication.

# CHAPTER 5: CHANGES IN THIAZOLIDINEDIONE USE AND OUTCOMES FOLLOWING REMOVAL OF A PRIOR AUTHORIZATION POLICY: CONTROLLED TIME-SERIES ANALYSIS

## 5.1 Introduction

Prior authorization policies are commonly used by drug insurance plans in the United States and Canada to curb spending on newer, and typically more expensive, on-patent drugs.[1,2] Most prior authorization policies limit reimbursement to patients fulfilling pre-specified clinical criteria, such as failing first line therapy. Studies evaluating prior authorization policies suggest that they are often cost saving for drug plans, and may or may not have negative health consequences. In fact, there is conflicting evidence suggesting that prior authorization policies have no effect,[3-6] are harmful,[7,8] or are even beneficial on clinical outcomes.[9] Furthermore, several systematic reviews have identified the urgent need for rigorously conducted studies evaluating short and long term effects of prior authorization policies on both drug use and clinical outcomes – both their introduction and their withdrawal.[1,10-15]

While most studies evaluating prior authorization have focused on introduction of the policy, few have evaluated their removal.[10] McCombs et al studied the impact of the removal of a prior authorization policy for two selective serotonin reuptake inhibitors (SSRI), fluoxetine and paroxetine, in California.[16,17] They found an increase in SSRI use (primarily fluoxetine and paroxetine) and a decrease in the proportion of patients who completed six months of continuous antidepressant therapy following the policy change. A study evaluating the removal of a prior authorization policy for histamine receptor antagonists and proton pump inhibitors in Belgium concluded that the intended effect to drive prescribing toward less expensive medications was not successful.[18] O'Reilly et al found a substantial increase in the use and costs of atypical antipsychotic drugs without an expected decrease in hospital use following the removal of a prior authorization policy for these agents.[19,20] Limitations of these studies include the lack of clinical outcomes and external controls to account for secular trends in patterns of prescribing or changes in case-mix over time.

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Thiazolidinediones (TZDs), a class of diabetes drugs introduced in the late 1990's,were quickly adopted and soon accounted for over 30% of office-based diabetes prescriptions.[21] At the time of their introduction, many drug insurance plans initially attempted to limit the use of TZDs through prior authorization policies; however, some jurisdictions subsequently removed these policies. Removal of policies may increase drug expenditures (expected) and may lead to positive or negative health consequences but to date policy-attributable effects (PAE) have been difficult to discern or even study. TZDs would be an ideal class of drugs to examine this issue since jurisdictions differed in when they implemented/removed prior authorization policies for these drugs and evidence now indicates that there is an increased risk of adverse cardiovascular events (particularly myocardial infarction and heart failure) with these agents.[22]

Therefore, we took advantage of a natural policy experiment of prior authorization in two adjacent Canadian provinces: one province (Alberta) acted as the intervention (TZD prior authorization policy rescinded in 2003-2004) while another (Saskatchewan) acted as a control because the TZD prior authorization policy remained in place. We hypothesized that removal of TZD prior authorization would lead to increased TZD use in Alberta (vs. Saskatchewan controls) and would lead to greater adverse clinical events in Alberta (vs. Saskatchewan controls).

## 5.2 Methods

### *Study Population*

We conducted a controlled interrupted time-series study using administrative data from the adjacent Canadian provinces of Alberta and Saskatchewan. Briefly, both provinces are located in Western Canada and provide universal health insurance for the approximately 3.5 million residents in Alberta and one million residents in Saskatchewan. Using a de-identified unique number, we linked individual level health utilization data for hospitalizations, ambulatory care, physician visits, and outpatient pharmacy dispensations from both provinces. The province of Alberta provides outpatient drug

insurance for residents 65 years and older as well as individuals and families with low incomes. Saskatchewan provides drug insurance to virtually all residents irrespective of age or income.

Our study population consisted of new users of oral antidiabetic agents 66 years of age or older in Alberta and Saskatchewan based on their first claim between January 1, 2001 and December 31, 2005. New use was defined as no use of insulin or an oral antidiabetic drug in the previous year. Individuals remained in the cohort until they left the province, died, or December 31, 2006, whichever occurred first. The Health Research Ethics Board at the University of Alberta approved this study.

***TZD Policies in Alberta (Intervention)***

The TZDs, pioglitazone and rosiglitazone, were listed on Alberta's public drug plan formulary under a prior authorization policy as of December 1, 2000 and January 1, 2001 respectively. These agents were authorized for coverage for patients with type 2 diabetes who were not adequately controlled with, were intolerant to, or had a contraindication for metformin or sulfonylureas. On December 1, 2003 and February 1, 2004, the prior authorization policy was removed for rosiglitazone and pioglitazone, respectively, and they were available as a full benefit with no restrictions on Alberta's public drug plan formulary.

***TZD Policies in Saskatchewan (Controls)***

In the neighboring province of Saskatchewan, rosiglitazone and pioglitazone were introduced onto the provincial formulary in August 2000 and April 2001, respectively. The prior authorization policy for these drugs was similar to Alberta's, whereby a patient must have previously failed to achieve adequate glucose control or be intolerant to metformin and sulfonylurea therapy before the TZD would be covered. However, unlike Alberta, Saskatchewan never removed their TZD prior authorization policy during the study period of interest.

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***Study Outcomes***

The outcomes measured included drug utilization and clinical outcomes. Our primary drug utilization measure of interest was TZD use within 30 days of entering the cohort. Secondary drug utilization outcomes included TZD use within 365 days, and metformin, sulfonylurea, or insulin use within 30 days and 365 days of cohort entry. We also calculated the mean number of prescriptions for diabetes treatments per person per month as a proxy for treatment intensity.

Our primary clinical outcome was a composite of all-cause mortality, hospitalization for an acute coronary event, or hospitalization for heart failure within 365 days of cohort entry. Secondary clinical outcomes included components of the composite outcome, hypoglycemic events, and bone fractures (a noted adverse effect of TZDs)[23] within 365 days of cohort entry. We also assessed changes in healthcare utilization by measuring all-cause hospitalization visits within 30 days and 365 days of cohort entry. International classification of disease (ICD) codes were used to identify all clinical outcomes (Table 5-1).

***Statistical Analysis***

Cohort characteristics before and after the removal of Alberta's prior authorization policy for TZDs were compared in Alberta and Saskatchewan using chi-squared, t-tests, or non-parametric tests, as appropriate. For the interrupted time-series analysis, individual level data was aggregated into 58 monthly intervals, 35 intervals before and 23 intervals after the prior authorization removal for TZDs. A unique group of new users of antidiabetic drugs was identified within each interval and outcomes per 100 individuals during each interval were calculated. To evaluate changes in the level and trend of drug utilization and clinical outcomes after the removal of the prior authorization policy we used segmented linear regression models.[24]

We tested a parsimonious model and an adjusted model for each outcome. For our parsimonious model we included linear trend variables to represent the period of time

before and after the policy change. For our adjusted model we also included: age, sex, previous diagnosis of heart failure, ischemic heart disease, myocardial infarction, stroke, hypertension, arrhythmia, angina, chronic pulmonary disease, cancer, kidney disease, and use of cardiac medications (statins, beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, thiazide and loop diuretics, dihydropyridine and non-dihydropyridine calcium channel blockers, warfarin, and clopidogrel) in the year prior to initial diabetes therapy.

We excluded ("interrupted") the 2-month time period between the removal of rosiglitazone (December 1, 2003) and pioglitazone (February 1, 2004) prior authorization policies from our analyses to ensure that the policy change was in place for both TZD agents (i.e., implementation period or phase-in/transition period).[24] To test for autocorrelation we used the Durbin-Watson test statistic and corrected for it and for clustering of patients within provinces using generalized estimating equations with a first-order autoregressive correlation structure.[24] Conceptually, we studied a natural policy experiment comparing intervention vs. control. Specifically, we included monthly observations from both the intervention (i.e., Alberta) and control (i.e., Saskatchewan) provinces within our statistical models and directly estimated the PAE through the interaction term for province and level change immediately following the removal of the prior authorization policy. This interaction term represents the difference in the percentage change in the outcomes between intervention and control populations and was used to estimate PAE.[25] We also tested the interaction term for province and change in slope for all outcome variables; these terms were either not statistically significant or of marginal magnitude to be important, and therefore have not included these in our main analysis (data available from authors). Analyses were conducted using Stata/SE Version 11.2 (StataCorp LP, College Station, TX).

## 5.3 Results

We identified 22,441 individuals in Alberta and 6,682 individuals in Saskatchewan who were 66 years of age and older and new users of oral diabetes therapy between January 2001 and December 2005 (Table 5-2). Compared to Saskatchewan (controls), the Alberta study population was younger (75 years vs. 76 years), more likely to be female (52% vs. 49%), less likely to hospitalized (22% vs. 40%) but more likely to have an emergency department visit (35% vs. 8%) within the year prior to cohort entry. The use of cardioprotective medications such as ACE inhibitors, ARBs, and statins in the year prior to initiating diabetes treatment was higher in the Alberta population compared to Saskatchewan controls. Demographics and comorbidities were comparable before and after the policy change timeframes in both provinces (Table 5-2).

***Changes in drug utilization***

Figures 5-1a through 5-1d illustrate the observed and expected use for all anti-diabetic treatments between January 2001 and December 2005. For the TZDs, which were directly affected by the policy in Alberta, the mean time to first use of a TZD decreased from 791 days before the policy change to 161 days after the policy change ($p<0.001$). Similarly, the mean time to first use of a TZD decreased in the control population of Saskatchewan from 1082 days to 418 days ($p<0.001$). Any use of TZDs within 30 days of initiation of diabetes treatment (Figure 5-1a; Table 5-3) increased 9.1% (95% confidence interval (CI) 7.4%-10.8%, $p<0.001$) immediately after the prior authorization policy was removed in Alberta and by 10.1% (95% CI 7.5%-12.7%) within 365 days. Conversely, no significant increase was observed in Saskatchewan (control) following Alberta's policy change for TZD use at 30 days (0.04% level change, 95% CI -1.4%-1.4%, $p=0.96$) or 365 days (0.3%, 95% CI -1.7%-2.4%, $p=0.76$). Comparing changes between Alberta and Saskatchewan following the removal of the restricted policy for the use of TZDs in Alberta showed that the policy-attributable effect was significant for TZD use at 30 days (9.1% adjusted absolute increase, 95% CI 7.0%-

11.2%, p<0.001) and 365 days (9.8% adjusted absolute increase, 95% CI 6.6%-12.9%, p<0.001). We did not observe any significant changes in the slope or trends of the PAE for antidiabetic drug utilization.

Despite the increasing use of TZDs in Alberta, there was no statistically significant change in the mean number of prescriptions for diabetes medications per period following the policy change in either Alberta or Saskatchewan (Table 5-3). Conversely, use of any of metformin, sulfonylurea, or insulin collectively decreased by 5.6% at 30 days and 4.9% by 365 days in Alberta, suggesting that the increased use of TZDs following removal of a prior authorization policy was countered by a reduction in the use of other diabetes medications (i.e., a pattern of substitution rather than addition and increased treatment intensity).

***Effect on clinical outcomes***

There was no statistically significant change in the proportion of patients who experienced all-cause mortality, hospitalization for ACS, heart failure within 365 days or the composite of these 3 variables after the prior authorization policy removal in Alberta, (p=0.33, Table 2) nor in Saskatchewan (p=0.75, Table 5-3). There were also no significant PAE differences in hypoglycemia events (p=0.13) or fractures (p=0.33) observed between Alberta and the Saskatchewan controls.

## 5.4 Discussion

In a natural policy experiment undertaken in two adjacent Canadian provinces, we found that the removal of a prior authorization policy for TZDs was associated with a statistically significant 9.1% adjusted absolute increase in any TZD utilization within 30 days that persisted for up to 1-year – changes that were not seen in the control province that had an ongoing prior authorization program. Despite an immediate and sustained increase in TZD use following the policy change in the intervention province, the overall use of diabetes drugs did not change and the use of other diabetes drugs decreased. Therefore, the removal of the prior authorization requirement for TZDs appeared to shift

the pattern of prescribing, whereby TZDs were used in place of metformin and sulfonylureas.

Importantly, we did not observe evidence of population-level harms as a result of the policy change in either the short-term or long-term. In fact, and somewhat surprisingly, we observed no differences in acute coronary syndromes or heart failure hospitalizations with an increase in the use of TZDs after the prior authorization policy was rescinded. Despite clinical trial evidence supporting an increased risk of heart failure with TZDs,[26] we failed to observed any change in hospitalization for heart failure. This may be due to selection bias or channeling whereby prescribers may have preferentially avoided TZDs in patients at higher risk for heart failure or with less severe heart failure because of early signals from RCTs associating TZDs with ankle swelling and new onset heart failure.[26] Moreover, healthier patients may have been given TZDs due to easier access, thereby introducing a healthy user bias. Alternatively, maybe sulfonylureas are more cardio-toxic than previously thought and the apparent null effect on heart failure with an increase in TZD use is because they are replacing sulfonylureas, although this is a hypothesis that requires testing. Regardless, this natural experiment confirmed one hypothesis (increased TZD use) but it refuted the other (increased adverse events), perhaps illustrating how important such controlled evaluations of policy are.

Although we used a quasi-experimental controlled interrupted time-series design, which is a robust approach to testing policy effects, there are several limitations to consider when interpreting the results of this study. First, our measures of drug use were calculated from administrative claims data limited to capturing drugs that were benefits under each provincial drug insurance plan. TZD use was substantially lower in the control population even in the pre-policy change period. However, the use of a time-series approach, that examines both changes in level and trend, greatly mitigates these types of differences and permits some degree of control over such characteristics.

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Second, the ability to test for differences in less severe hypoglycemic events would be under captured due to the reliance on healthcare encounters. Third, there may have been co-interventions or competing secular trends that we are not aware of that were distributed differently across the intervention and control provinces. Fourth, one year of follow-up may not have been sufficient to capture clinical outcomes such as acute coronary events, although studies less than 12 months have found a high risk of heart failure associated with TZDs.[26] Last but most important, we did not have information on clinical variables that may affect treatment selection and outcomes such as hemoglobin A1c, serum creatinine, dyspnea, ankle swelling, or left ventricular ejection fraction. However, there is no reason to believe that the physicians in the two adjacent provinces would respond to such variables in a different manner.

We found that the removal of a prior authorization policy for TZD coverage in the province of Alberta was associated with a significant increase in use of TZDs but did not adversely impact population-level clinical outcomes. Our results suggest that prior authorization policies not only control drug use, and by extension costs, while in place but also may influence prescribing practices. As we have shown, by rescinding a prior authorization policy, treatments with a more robust evidence base for morbidity and mortality outcomes[27] (metformin and sulfonylureas) may be replaced with treatments with greater uncertainty of benefits and risks (TZDs). However, our finding that clinical outcomes did not appreciably change despite increased use of TZDs in Alberta suggests that clinicians channeled their use of TZDs in Alberta to patient sub-populations at lower risk of the adverse effects we studied. Regardless, the removal of prior authorization policies for new therapies with an uncertain risk-benefit profile may not be favourable in the absence of such channeling. We would suggest that prior authorizations are a reasonable approach toward safe guarding public health especially for chronic disease where other therapies with a more robust evidence base are available.

A version of this chapter has been submitted for publication.

## Table 5-1. International Classification of Diseases Codes used to Identify Clinical Outcomes

| Outcome | ICD-9 CM Code | ICD-10 CA Code |
|---|---|---|
| All-cause mortality | n/a | n/a |
| Acute coronary event | | |
| Acute myocardial infarction | 410 | I21.x |
| Unstable angina | 411 | I20.0 |
| Cardiac arrest | 427.5 | I46.x |
| Heart failure | 428.x | I50.x |
| Hypoglycemic events | 251.0;<br>251.1;<br>251.2;<br>250.8 | E16.0-E16.2 |
| Fractures | 800.x-829.x | S12;<br>S22.0;<br>S22.1;<br>S22.2-S22.9;<br>S32.0;<br>S32.1-S32.8;<br>S02;<br>S62<br>S72;<br>S82;<br>S92;<br>M48.4;<br>M48.5;<br>M80.0;<br>M80.9 |

**Table 5-2. Patient Characteristics of New-Users of Oral Diabetes Agents in Alberta (Intervention) and Saskatchewan (Control), Canada, 2001 to 2005.**

| | Alberta (Intervention) | | Saskatchewan (Control) | |
|---|---|---|---|---|
| Variable | Prior Authorization Period: Jan. 2001 to Nov. 2003 (n=8,859) | Regular Benefit Period: Feb. 2004 to Dec. 2005 (n=13,582) | Prior Authorization Period: Jan. 2001 to Nov. 2003 (n=3,886) | Prior Authorization Period: Feb. 2004 to Dec. 2005 (n=2,796) |
| Age, mean (sd) | 75 (6) | 75 (6) | 76 (7) | 76 (7) |
| Female (%) | 52 | 52 | 48 | 50 |
| ≥1 Hospitalization in the year prior to index (%) | 23 | 21 | 41 | 40 |
| Pre-existing illness (%) | | | | |
| Acute myocardial infarction | 6 | 5 | 4 | 4 |
| Ischemic heart disease | 17 | 17 | 20 | 18 |
| Congestive heart failure | 10 | 9 | 13 | 11 |
| Cerebrovascular disease | 6 | 5 | 6 | 5 |
| Hypertension | 56 | 59 | 56 | 60 |
| Dysrhythmia | 24 | 23 | 11 | 11 |
| Renal Failure | 3 | 4 | 3 | 2 |
| Cancer | 7 | 7 | 6 | 5 |
| Medication Use in the year prior to index (%) | | | | |
| ACE-I | 71 | 66 | 35 | 37 |
| ARB | 37 | 37 | 13 | 19 |
| Beta-blocker | 22 | 26 | 22 | 26 |
| Statin | 24 | 36 | 19 | 30 |
| Clopidogrel | 2 | 3 | 2 | 4 |
| Diabetes agents within 30 days of index date (%) | | | | |
| Metformin | 69 | 80 | 73 | 90 |
| Sulfonylurea | 36 | 15 | 35 | 15 |
| Thiazolidinedione | 3 | 13 | 1 | 2 |
| Glinide | 5 | 4 | 0.3 | 0.5 |
| Acarbose | 0.8 | 0.3 | 0.7 | 0.3 |
| Insulin | 1 | 1 | 1 | 1 |

**Table 5-3. Changes in Drug Utilization, Healthcare Utilization, and Clinical Outcomes and Policy-Attributable Effect From Before to After the Removal of a Prior Authorization Policy**

| | Level Change | | Policy-Attributable Effect | |
|---|---|---|---|---|
| Variable | AB | SK | Difference in level change (95% CI) | P-Value |
| ***Drug Utilization*** | | | | |
| **Short-term (30-day) outcomes** | | | | |
| Thiazolidinedione Use (%) | 9.1 | 0.04 | 9.1 (7.0 - 11.2) | <0.01 |
| Metformin, sulfonylurea, or insulin Use (%) | -5.6 | -0.5 | -5.2 (-7.3 - -3.0) | <0.01 |
| Metformin Use (%) | -4.1 | 0.4 | -4.4 (-10.6 - 1.8) | 0.16 |
| Sulfonylurea Use (%) | -4.7 | -1.2 | -3.5 (-10.5 - 3.5) | 0.33 |
| Insulin Use (%) | 0.1 | -0.5 | 0.6 (-0.8 - 2.0) | 0.4 |
| Mean number of prescriptions for diabetes per person | 0.040 | 0.02 | 0.02 (-0.13 - 0.16) | 0.83 |
| **Long-term (365-day) outcomes** | | | | |
| Thiazolidinedione Use (%) | 10.1 | 0.3 | 9.8 (6.6 - 12.9) | <0.01 |
| Metformin, sulfonylurea, or insulin Use (%) | -4.9 | -0.5 | -4.5 (-6.6 - -2.4) | <0.01 |
| Metformin Use (%) | -4.5 | 0.3 | -4.8 (-10.7 - 1.2) | 0.12 |
| Sulfonylurea Use (%) | -3.8 | -1.3 | -2.5 (-9.6 - 4.7) | 0.50 |
| Insulin Use (%) | 1.5 | 0.1 | 1.4 (-0.8 - 3.6) | 0.21 |
| Mean number of prescriptions for diabetes per person | 0.1 | 0.008 | 0.1 (-0.7 - 1.0) | 0.79 |
| ***Healthcare Utilization*** | | | | |
| **Short-term (30-day) outcomes** | | | | |
| All-cause hospitalization (%) | -1.6 | 0.09 | -1.7 (-4.9 - 1.5) | 0.3 |
| **Long-term (365-day) outcomes** | | | | |
| All-cause hospitalization (%) | -0.1 | 4.2 | -4.4 (-10.2 - 1.4) | 0.14 |
| ***Clinical Events*** | | | | |
| Composite of all-cause mortality and hospital admission for acute coronary syndrome or heart failure | -1.8 | -0.4 | -1.4 (-5.6 - 2.9) | 0.53 |
| All-cause mortality | -0.7 | -2.4 | 1.7 (-1.0 - 4.5) | 0.22 |
| Admission for acute coronary syndrome | 0.7 | 1.7 | -0.9 (-3.0 - 1.2) | 0.39 |
| Acute myocardial infarction | -0.1 | 1.3 | -1.4 (-3.4 - 0.5) | 0.15 |
| Unstable angina | 0.3 | 0.4 | -0.03 (-1.8 - 1.7) | 0.97 |
| Cardiac arrest | 0.4 | 0.02 | 0.4 (-0.3 - 1.1) | 0.27 |
| Admission for heart failure | -0.5 | 1.8 | -2.3 (-5.6 - 1.0) | 0.17 |

Note: Results are adjusted for age, sex, previous diagnosis of heart failure, ischemic heart disease, myocardial infarction, stroke, hypertension, arrhythmia, angina, chronic pulmonary disease, cancer, kidney disease, use of cardioprotective medications (statins, beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, thiazide and loop diuretics, dihydropyridine and non-dihydropyridine calcium channel blockers, warfarin, and clopidogrel) in the year prior to initial diabetes therapy.

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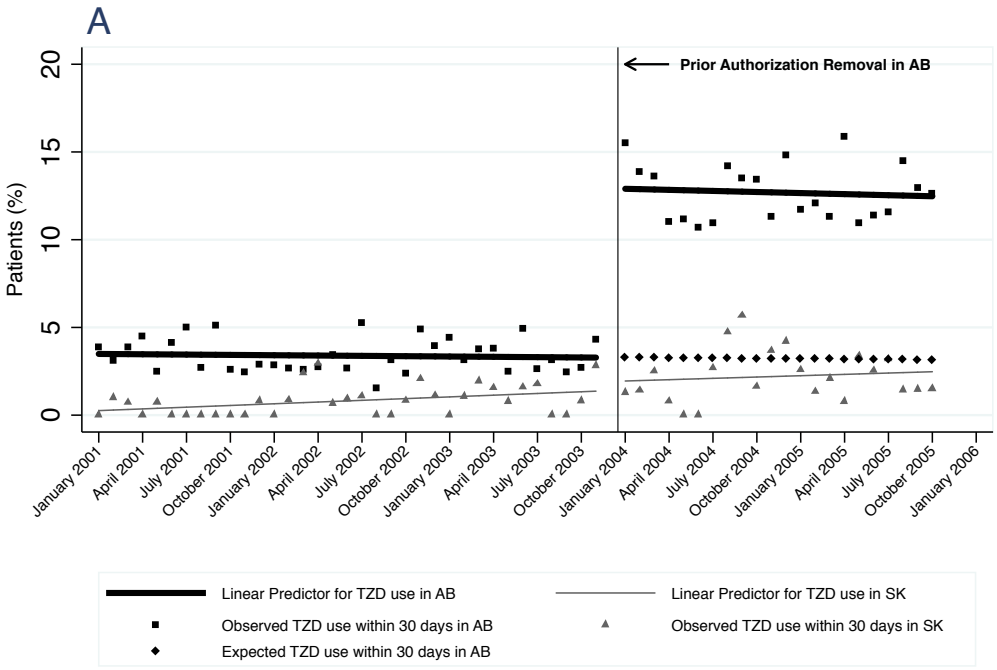
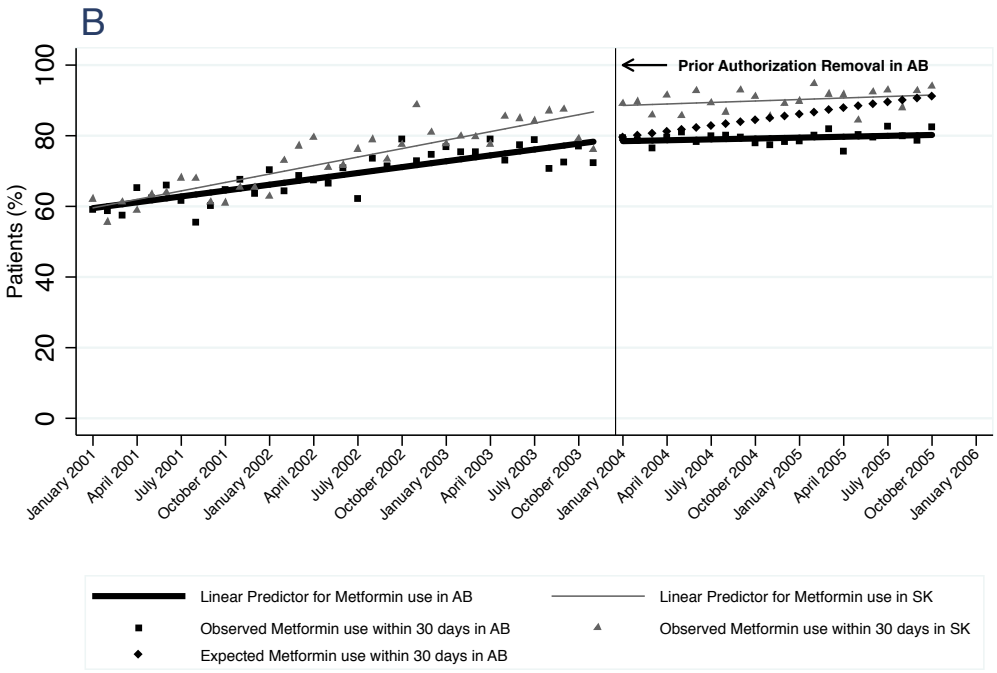
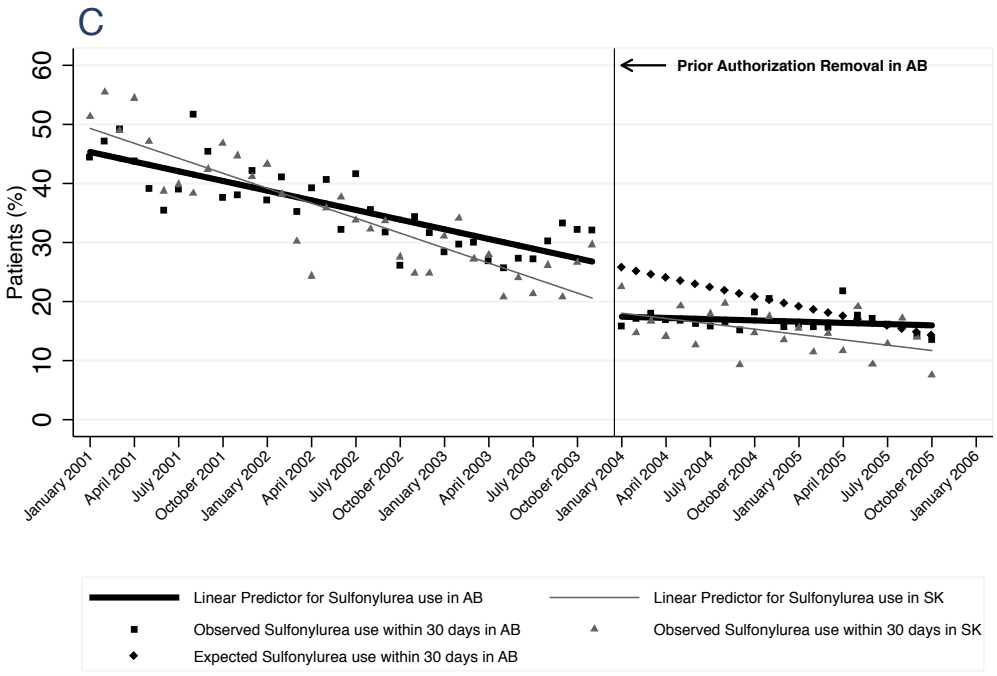
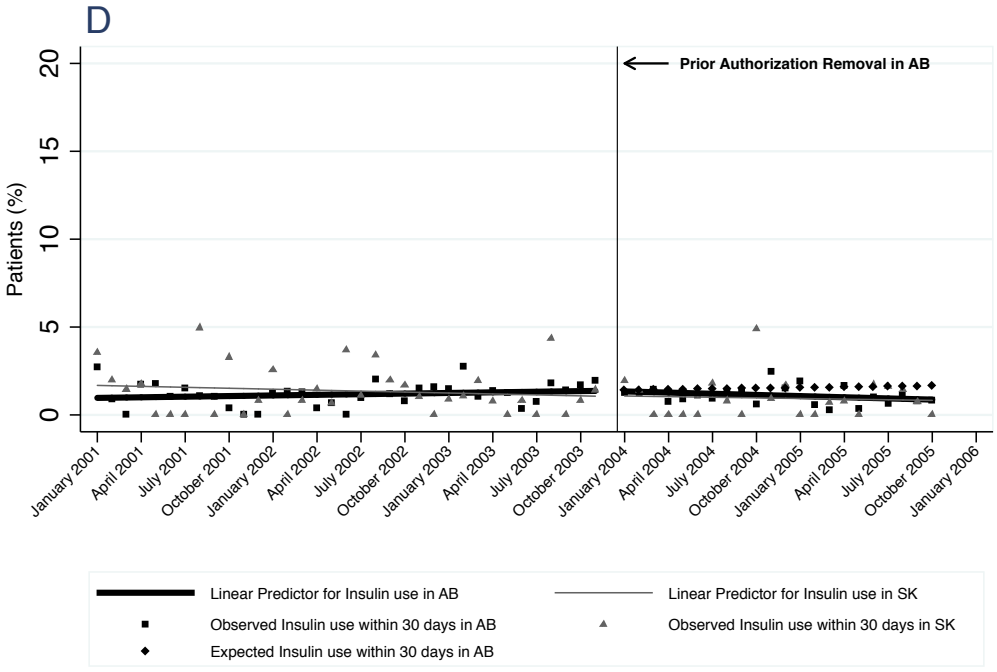
**Figure 5-1. Percent of New Users of Oral Diabetes Agents Initiating Thiazolidinedione Therapy (Panel A), Metformin Therapy (Panel B), Sulfonylurea Therapy (Panel C), or Insulin Therapy (Panel D) within 30 days in Alberta and Saskatchewan, 2001-2005.**




C
Prior Authorization Removal in AB
Patients (%)
0
10
20
30
40
50
60
January 2001
April 2001
July 2001
October 2001
January 2002
April 2002
July 2002
October 2002
January 2003
April 2003
July 2003
October 2003
January 2004
April 2004
July 2004
October 2004
January 2005
April 2005
July 2005
October 2005
January 2006
Linear Predictor for Sulfonylurea use in AB
Linear Predictor for Sulfonylurea use in SK
Observed Sulfonylurea use within 30 days in AB
Observed Sulfonylurea use within 30 days in SK
Expected Sulfonylurea use within 30 days in AB


D
Prior Authorization Removal in AB
Patients (%)
0
5
10
15
20
January 2001
April 2001
July 2001
October 2001
January 2002
April 2002
July 2002
October 2002
January 2003
April 2003
July 2003
October 2003
January 2004
April 2004
July 2004
October 2004
January 2005
April 2005
July 2005
October 2005
January 2006
Linear Predictor for Insulin use in AB
Linear Predictor for Insulin use in SK
Observed Insulin use within 30 days in AB
Observed Insulin use within 30 days in SK
Expected Insulin use within 30 days in AB

## 5.5 References

1. MacKinnon NJ. Prior authorization programs: a critical review of the literature. *J Manag Care Pharm* 2001;7:297-302.

2. Hamel MB, Epstein AM. Prior-authorization programs for controlling drug spending. *N Engl J Med* 2004;351:2156-2158.

3. Delate T, Mager DE, Sheth J, Motheral BR. Clinical and financial outcomes associated with a proton pump inhibitor prior-authorization program in a Medicaid population. *Am J Manag Care* 2005;11:29-36.

4. Schneeweiss S, Maclure M, Carleton B, Glynn RJ, Avorn J. Clinical and economic consequences of a reimbursement restriction of nebulised respiratory therapy in adults: direct comparison of randomised and observational evaluations. *BMJ* 2004;328:560.

5. Marshall D, Simonyi S, McGeer A, et al. Impact of antibiotic administrative restrictions on trends in antibiotic resistance. *Can J Public Health* 2006;97:126-131.

6. Guenette L, Gaudet M. Impact of prior authorization for asthma medications on the use of emergency health services: a retrospective cohort study among newly diagnosed patients with asthma. *Clin Ther* 2010;32:965-972.

7. Jackevicius C, Tu J, Demers V, et al. Cardiovascular outcomes after a change in prescription policy for clopidogrel. *N Engl J Med* 2008;359:1802-1810.

8. Sheehy O, LeLorier J, Rinfret S. Restrictive access to clopidogrel and mortality following coronary stent implantation. *CMAJ* 2008;178:413-420.

9. Mamdani M, Warren L, Kopp A, et al. Changes in rates of upper gastrointestinal hemorrhage after the introduction of cyclooxygenase-2 inhibitors in British Columbia and Ontario. *CMAJ* 2006;175:1535-1538.

10. Green C, Maclure M, Fortin P, Ramsay C, Aaserud M, Bardal S. Pharmaceutical policies: effects of restrictions on reimbursement. *Cochrane Database of Systematic Reviews* 2010;Issue 8:Art. No.: CD008654. DOI: 008610.001002/14651858.CD14008654.

A version of this chapter has been submitted for publication.

11. Carlton R, Bramley T, Nightengale B, Conner T, Zacker C. Review of Outcomes Associated With Formulary Restriction: Focus on Step Therapy. *Am J Pharm Benefits* 2010;2:50-58.

12. Morrison A, MacKinnon N, Hartnell N, McCaffrey K. Impact of drug plan management policies in Canada: A systematic review. *Can Pharm J* 2008;141:332-338.

13. Puig-Junoy J, Moreno-Torres I. Impact of pharmaceutical prior authorisation policies : a systematic review of the literature. *Pharmacoeconomics* 2007;25:637-648.

14. Soumerai SB. Benefits and risks of increasing restrictions on access to costly drugs in Medicaid. *Health Aff (Millwood)* 2004;23:135-146.

15. Lexchin J. Effects of restrictive formularies in the ambulatory care setting. *Am J Manag Care* 2002;8:69-76.

16. McCombs JS, Shi L, Stimmel GL, Croghan TW. A retrospective analysis of the revocation of prior authorization restrictions and the use of antidepressant medications for treating major depressive disorder. *Clin Ther* 2002;24:1939-1959.

17. McCombs JS, Shi L, Croghan TW, Stimmel GL. Access to drug therapy and substitution between alternative antidepressants following an expansion of the California Medicaid formulary. *Health Policy* 2003;65:301-311.

18. van Driel ML, Vander Stichele R, Elseviers M, De Sutter A, De Maeseneer J, Christiaens T. Effects of an evidence report and policies lifting reimbursement restrictions for acid suppressants: analysis of the Belgian national database. *Pharmacoepdiemiol Drug Saf* 2008;17:1113-1122.

19. O'Reilly DJ, Goeree RA, Tarride J-E, James C, Parfrey PS. The unintended (and costly) effects due to the introduction of an unrestricted reimbursement policy for atypical antipsychotic medications in a Canadian public prescription drug program: 1996/97 to 2005/06. *Can J Clin Pharmacol* 2009;16:e346-359.

20. O'Reilly D, Craig D, Phillips L, Goeree R, Tarride JE, Parfrey P. Costs of new atypical antipsychotic agents for schizophrenia: does unrestricted access reduce hospital utilization? *Healthc Policy* 2007;3:58-79.

A version of this chapter has been submitted for publication.

21. Cohen A, Rabbani A, Shah N, Alexander G. Changes in Glitazone Use Among Office-Based Physicians in the U.S., 2003-2009. *Diabetes Care* 2010;33:823-825.

22. Cohen D. Rosiglitazone: what went wrong? *BMJ* 2010;341:c4848.

23. Loke YK, Singh S, Furberg CD. Long-term use of thiazolidinediones and fractures in type 2 diabetes: a meta-analysis. *CMAJ* 2009;180:32-39.

24. Wagner A, Soumerai S, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. *J Clin Pharm Ther* 2002;27:299-309.

25. Law M, Majumdar S, Soumerai S. Effect of illicit direct to consumer advertising on use of etanercept, mometasone, and tegaserod in Canada: controlled longitudinal study. *BMJ* 2008;337:a1055.

26. Hernandez AV, Usmani A, Rajamanickam A, Moheet A. Thiazolidinediones and risk of heart failure in patients with or at high risk of type 2 diabetes mellitus: a meta-analysis and meta-regression analysis of placebo-controlled randomized clinical trials. *Am J Cardiovasc Drugs* 2011;11:115-128.

27. Holman R, Paul S, Bethel M. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008;359:1577-1589.

A version of this chapter has been submitted for publication.

# CHAPTER 6: SUMMARY

## 6.1 Summary of Research

Pharmacoepidemiologists use observational study designs to tease out potential benefits and risks of drugs by carefully analyzing data generated from everyday healthcare encounters. Valid study results rely on high quality data sources that accurately capture individual level healthcare information including drug exposure, hospitalizations, emergency department and physician visits. However an important, yet poorly understood, source of data inaccuracy relates to *restrictive drug coverage polices*.

The influence of restrictive drug coverage policies on the validity of observational drug studies using administrative data has been understudied. To address this information gap, several inter-related studies were undertaken to enhance our knowledge and understanding in this area. This research is timely and extremely important as health scientists, drug regulators, and health care professionals around the globe are increasingly relying on the use of administrative healthcare databases to answer questions of drug safety and effectiveness.

The overall objective of the program of research was to measure the impact of restrictive drug coverage policies on the magnitude and direction of potential bias within administrative databases due to restrictive drug coverage policies. This objective was accomplished through three inter-related studies using various administrative drug data sources. Upon completion of these studies, it was clear misclassification bias due to restricted drug coverage polices has the potential to introduce significant bias in clinical studies. However, it was also evident that irrespective of presence or absence of misclassification bias, restricted drug policies themselves may have significant unintended clinical consequences at the population level. As a result, a second major initiative of the program of research was to specifically examine the impact of a restrictive drug coverage policy that was removed and the resulting consequences on population outcomes.

Misclassification bias is a serious threat to the validity of any observational study evaluating the relationship between an exposure and outcome.[1] Accurate measurement of drug exposure is essential to avoid such misclassification bias. Although administrative databases avoid recall bias and are generally one of the most reliable sources of drug exposure information, they may be missing drug exposure information for certain drugs with restrictive coverage policies. Previous research has suggested misclassification of drug exposure through missing data as a result of restrictive drug coverage policies may be occurring in a variety of administrative datasets.[2-5] Building on this previous research the objective of the first three studies was to better understand the problem of missing drug exposure information for patients exposed to drugs subject to a restrictive coverage policy and how this may influence the validity of typical administrative observational drug studies.

Although it is generally believed that the extent of missing drug information in many administrative healthcare databases is minimal and inconsequential, our results suggest otherwise. Using a macro-level descriptive analyses, we found on average that drugs with a restrictive coverage policy had a 40% absolute lower capture rate within one of the most widely used and accepted drug administrative databases, compared to drugs with no coverage restrictions (Chapter 2). Further, this discrepancy was observed across seven major therapeutic drug classes for both acute and chronic conditions. To our knowledge, our study is one of the first to directly quantify the extent of missing drug exposure information by drug coverage status. Previous studies have either focused on private drug insurance use or merely reported a statement regarding the extent of non-benefit drug use.[2,4,5]

Following this observation, we further explored the nature of potential bias introduced by exposure misclassification through a series of simulations (Chapter 3). Many have argued that misclassification introduced by missing drug information within administrative databases would be most likely be non-differential and therefore bias risk estimates toward the null.[6] Although this may be true in some circumstances, restrictive

drug polices are in fact most likely to introduce differential misclassification. Through a series of simulations we demonstrated that two common restrictive drug coverage policies, a non-formulary policy and prior authorization policy, may introduce significant drug exposure misclassification in administrative claims data and thereby bias reported drug-outcome associations (Chapter 3).[7] Indeed, our simulation demonstrated the potential for a change in the direction of the association, from one of apparent benefit to one of apparent harm. Further, even small degrees of bias in studies with marginal statistically significant results are observed may alter study interpretation (i.e., shift statistically significant results to non-significant). Although acknowledged, this potential impact on study results is rarely given serious consideration in the interpretation of observational studies using administrative data where restrictive drug policies may have been in place.

Although our simulation study strongly supports the potential for misclassification bias in administrative databases with restrictive drug polices, whether these effects are observed in real-world data is less certain. Thus, using a real-world cohort of diabetic patients derived from Saskatchewan Health data, we evaluated several drugs that were potentially under captured in the administrative data because of a prior authorization policy (Chapter 4). These drugs included the diabetes drugs pioglitazone and rosiglitazone (thiazolidinediones [TZD]), the antithrombotic drug clopidogrel, and the beta-blockers bisoprolol and carvedilol.

We found that among patients with diabetes, 28% of TZD users, 24% of clopidogrel users, and 42% of carvedilol or bisoprolol users would have been misclassified as non-users in a typical administrative dataset limited by capturing benefit drugs only. Of note, the degree of under capture of these restricted drugs is consistent to our results observed in our macro-level analysis (Chapter 2), providing more empiric evidence for the under capture of drugs in administrative data subject to restricted drug polices. Importantly, we also observed that misclassified persons were less likely to be hospitalized or die compared to patients who did not have their drug exposure

misclassified; documenting the potential for selection bias to creep into a study analyzing a drug-outcome relationship involving one of the drug's of interest being subject to a restrictive drug policy. Importantly, we found that after adjustment for most major confounders within administrative data, a statistically significant yet clinically unimportant degree of bias was introduced into a typical observational drug study evaluating the association between drug exposure and hospitalization or death.

Collectively, the results of these studies suggest that missing drug exposure information for drugs with restrictive coverage policies is common; however, although simulation studies suggest a large degree of bias may be introduced, the potential within real-world data may not be sufficient to introduce enough bias to make a meaningful difference. Importantly, we only evaluated a small number of drug classes and restrictive drug policies. It is likely that the degree of misclassification bias introduced into a real-world observational study within administrative data is dependent on the nature of the drug policy (i.e., very restrictive criteria vs. less restrictive criteria), the population prevalence of the policy drug (i.e., a rarely used drug vs. a commonly used drug), how the drug is used in clinical practice (e.g., propensity for off-label use), the nature of the administrative database itself (e.g., all potential benefit drug dispensations captured vs. only drug dispensations paid for by the drug plan) and the degree of clinical difference in those using captured versus non-captured drugs. Indeed, our studies suggest the degree of bias introduced largely depends on the differences in clinical characteristics between patients using captured and non-captured drugs and administrative datasets that more fully capture these clinical differences may be less prone to bias through drug exposure misclassification.

As mentioned, the prevalence of use of the misclassified drug in the population is a key factor determining the degree of potential bias. For example, in our simulation study, over 60% of the population was using the drug of interest subject to a hypothetical restrictive coverage policy. However, a much smaller proportion of study subjects were using the policy drugs of interest in our real world cohort study of actual (non-

hypothetical) drug policies – 21% of the population were exposed to TZDs, 6% were exposed to clopidogrel, and only 1% were exposed to either carvedilol or bisoprolol; an even smaller portion were actually misclassified. In fact, in our study cohort of the approximately 30,000 patients with diabetes, less than 6% of patients had their TZD exposure misclassified and less than 1% of patients had their clopidogrel, bisoprolol or carvedilol misclassified. Therefore, the low prevalence of exposure misclassification within the entire cohort partially explains the small impact on study estimates that we reported. Our simulation study suggests that approximately 25% or more of the population would need to be affected. However, the problem in interpreting observational studies where restricted policy drugs have been evaluated is that it is almost impossible to determine (or at the very least is rarely reported) the actual number of patients using a non-captured drug.

Although restricted drug policies clearly affect the quality of data and interpretation of observational studies, another important question relates to the impact of these policies on the individuals who require these restricted drugs. There are important consequences of restrictive drug coverage polices beyond the validity of observational drug studies. These policies may impact the population's use of drugs, use of healthcare services, and ultimately the number of clinical events. Although some research has been conducted on the impact of the introduction of restricted drug polices, few studies have evaluated the impact of the removal of restricted drug coverage polices at the population level.[8]

We found that following the removal of a prior authorization policy for TZDs there was a significant increase in the use of rosiglitazone and pioglitazone and decreased use of other oral antidiabetic drugs such as metformin and sulfonylureas (Chapter 5). Despite concerns over the association between rosiglitazone and cardiovascular disease, we did not observe a shift in hospitalization for acute coronary events, heart failure, or death after the removal of the policy. Moreover, we observed a significant decrease in hypoglycemic events and fractures. Although this was contrary to our hypothesis in

which we expected an increased rate of heart failure related hospitalizations and fractures, a potential explanation for our findings includes selection bias or channeling. For example, prescribers may have given TZDs to patients at a lower risk for heart failure or with less severe heart failure because of early signals from RCTs associating TZDs with ankle swelling and new onset heart failure.[9] Similarly, healthier patients at a lower risk of fracture may have been preferentially prescribed TZDs. Evidence of TZD associated peripheral edema, heart failure, and fractures was being disseminated in the scientific and clinical literature throughout the period during which the policy change occurred, therefore potentially affecting prescribing habits around the time of the intervention.

Another explanation for why we did not observed an increase in heart failure is that the absolute number of heart failure cases associated with TZD use may have been relatively low compared to the total number of patients with diabetes, many of which may have been prescribed cardioprotective agents within the first year of diabetes treatment. Therefore any TZD related heart failure hospitalizations would potentially be outweighed by cardioprotective interventions that were not fully capture in our statistical model (i.e., interventions that occurred during the one year follow-up). In fact, the use of angiotensin converting enzyme inhibitors and statins increased significantly around the time that TZDs were introduced to the market and continued to be used more frequently through the policy change period.[10] Because the use of these cardioprotective agents were higher in the intervention group compared to the control throughout the study period, it is also possible that the effect of increased use of cardioprotective agents may be partially responsible for the lack of increased rate of heart failure related hospitalizations.

## 6.2 Implications for Future Policy

Drug policy makers are familiar with restrictive coverage policies and are ultimately interested in the cost-effective prescribing of drugs. However, because policy makers cannot foresee all potential consequences of a drug policy, it is imperative that

evaluation and surveillance of the introduction, change, or removal of a drug policy are conducted in a timely fashion. A research unit housed within the government's pharmaceutical policy branch or external collaboration with university based researchers using rigorous evaluative methods are ways in which this type of policy analysis could be brought to fruition. In addition, policy makers may not be aware of the potential downstream effect of these polices on research methods. It is through understanding this link that policy makers can help ensure they have the best access to unbiased research on drug safety and effectiveness. Moreover, because the majority of newly approved drugs are covered under a restrictive drug policy,[11] these issues are more and more relevant for policy makers.

Results from our program of research provide several lessons for drug policy makers in the context of research methods. First, designing administrative drug databases that contain all drug exposure information irrespective of drug coverage status is a critical role that policy makers must take to insure accurate and complete data for the evaluation of drugs and policies. In addition, ensuring researchers have timely access to these databases will aid in answering drug safety and effectiveness questions for drugs of interest to policy makers. Second, detailed reporting of drug policies including the dates of implementation, dates of any changes to criteria, and the reasons for coverage restrictions, will help inform researchers using databases that may be missing drug information due to these policies. This transparent reporting of drug policies may be carried out through monthly drug plan updates that are commonly produced across Canada for each public drug plan.

Another important policy implication from our research is that the effects of restrictive drug coverage policies must be systematically evaluated, using robust study designs, to understand their short- and long-term intended and unintended effects. Policy makers should consider implementing these types of studies or collaborating with academic researchers each time a new drug policy is introduced or a previous drug policy is removed. Unintended consequences of drug policies are never foreseeable; therefore,

only through rigorous surveillance can these effects be measured. Although we provide evidence that the removal of a prior authorization policy for TZDs resulted in a switching of use to TZDs from metformin and sulfonylureas without evidence of harm, the effects of drug policies may be specific to each class of drugs and geographic locale.[8]

## 6.3 Implications for Future Research

This program of research has important implications for those who conduct pharmacoepidemiology studies. Notably, initiatives such as Canada's Drug Safety and Effectiveness Network (DSEN), the United States' Sentinel Initiative, and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) will rely heavily on the use of automated administrative healthcare databases. These research networks will need to consider how restrictive drug coverage policies may affect their data collection methods, analysis, results and ultimately the interpretation of that data. Our work highlights that the details of the drug policies including the types of patients, which drugs, and over what time period are required to fully interpret results of pharmacoepidemiology studies. Also, our work shows the usefulness of macro-level descriptive analyses to check data integrity. We believe that governments, private drug insurers, HMO's, among others, must work in close collaboration with one another and researchers to more fully understand the nuances of drug specific drug policies and to be able to accurately incorporate this information into the research design, analysis and interpretation of studies.

In the context of our program of research, there are several areas that require future study. Understanding the predictors and outcomes of benefit and non-benefit drug users would be useful for determining potential confounding variables in the case of missing non-benefit drug dispensations. Also, identifying potential macro-level indicators or markers of misclassification through trend analysis of prescribing patterns. For example, if after the introduction of a restrictive drug coverage policy there were a reduction in the use of policy drugs but no observable shift in the use of non-policy drugs

within the same therapeutic class, this would suggest that non-benefit drug use might not be captured. Our work has focused on two Canadian provincial administrative databases and is not necessarily generalizable to other databases, especially private drug plans; however, virtually every government sponsored formulary system is implemented in a similar fashion to the provinces included in our analyses.

Future research should include measuring the extent of misclassification for other drugs and across multiple disease states and databases. Although this data may not be included in the administrative data itself, external sources of data like IMS, pharmacy information networks, as well as trend analysis (as suggested above) will allow researchers to at the very least identify misclassification in their analysis and conduct simulation sensitivity analyses of the potential impact of misclassified patients. Furthermore, this type of external validation work may contribute to conducting formal quantitative bias analysis to aid in understanding the influence of exposure misclassification within specific databases.[12] Both non-probabilistic and probabilistic models based on plausible values of exposure misclassification may be used to calculate bias-corrected effect estimates and can aid in interpretation of study results.[13] Plausible values of sensitivity and specificity of an exposure may be gathered from expert opinion or validation studies (external or internal).[14]

Future research in the area of drug policy evaluation is also necessary to ensure the introduction or removal of policies does not adversely affect patients. Drug policy evaluations must focus on all relevant outcomes including economic, clinical, and humanistic. There is almost complete lack of knowledge regarding the humanistic outcomes of drug policies.[15] Although difficult to study, more work on how to best study the long-term impact of drug policies on outcomes is essential. Further, this is an area where researchers could and perhaps should collaborate with policy makers.

## 6.4 References

1. Rothman K, Greenland S, Lash T. Validity in Epidemiologic Studies. In: Rothman KJ, Greenland S, Lash T, eds. *Modern Epidemiology*. third ed. Philadelphia: Lippincott Williams & Wilkins; 2008:128-147.

2. Paterson J, Suleiman A, Hux J, Bell C. How complete are drug history profiles that are based on public drug benefit claims? *Can J Pharmacol* 2008;15:e108-116.

3. Hennessy S, Bilker WB, Weber A, Strom BL. Descriptive analyses of the integrity of a US Medicaid claims database. *Pharmacoepdiemiol Drug Saf* 2003;12:103-111.

4. Dormuth C, Carney G, Carleton B, Bassett K, Wright J. Thiazolidinediones and Fractures in Men and Women. *Arch Intern Med* 2009;169:1395-1402.

5. Varas-Lorenzo C, Castellsague J, Stang M, Perez-Gutthann S, Aguado J, Rodriguez LA. The use of selective cyclooxygenase-2 inhibitors and the risk of acute myocardial infarction in Saskatchewan, Canada. *Pharmacoepdiemiol Drug Saf* 2009;18:1016-1025.

6. Lipscombe L, Gomes T, Lévesque L, Hux J, Juurlink D, Alter D. Thiazolidinediones and cardiovascular outcomes in older patients with diabetes. *JAMA* 2007;298:2634-2643.

7. Gamble J, McAlister F, Johnson J, Eurich D. Quantifying the Impact of Drug Exposure Misclassification Due to Restrictive Drug Coverage in Administrative Databases: A Simulation Study. *Value in Health* 2011;online October 19, 2011.

8. Green C, Maclure M, Fortin P, Ramsay C, Aaserud M, Bardal S. Pharmaceutical policies: effects of restrictions on reimbursement. *Cochrane Database of Systematic Reviews* 2010;Issue 8:Art. No.: CD008654. DOI: 008610.001002/14651858.CD14008654.

9. Hernandez AV, Usmani A, Rajamanickam A, Moheet A. Thiazolidinediones and risk of heart failure in patients with or at high risk of type 2 diabetes mellitus: a meta-analysis and meta-regression analysis of placebo-controlled randomized clinical trials. *Am J Cardiovasc Drugs* 2011;11:115-128.

10. Jackevicius CA, Cox JL, Carreon D, et al. Long-term trends in use of and expenditures for cardiovascular medications in Canada. *CMAJ* 2009;181:E19-28.

11. Gamble JM, Weir DL, Johnson JA, Eurich DT. Analysis of drug coverage before and after the implementation of Canada's Common Drug Review. *CMAJ* 2011;183:E1259-1266.

12. Greenland S, Lash TL. Bias Analysis. In: Rothman K, Greenland S, Lash T, eds. *Modern Epidemiology*. third ed. Philidelphia: Lippincott Williams & Wilkins; 2008:345-380.

13. Phillips CV. Quantifying and reporting uncertainty from systematic errors. *Epidemiology* 2003;14:459-466.

14. Jurek A, Lash TL, Maldonado G. Specifiying exposure classificaitno parameters for sensitivity analysis: family breast cancer history. *Clin Epidemiol* 2009;1:109-117.

15. Morrison A, MacKinnon N, Hartnell N, McCaffrey K. Impact of drug plan management policies in Canada: A systematic review. *Can Pharm J* 2008;141:332-338.