Pharmacological interventions in type 2 diabetes: observational studies and bias related issues

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ABSTRACT

Oral hypoglycemic agents are the treatment of first choice in the management of type 2 diabetes. Information available to date regarding the safety of these agents comes primarily from small, short-term, randomized controlled trials of highly selected populations that were powered to detect changes in plasma glucose. Consequently, concerns regarding their cardiovascular safety warrant further study using a population-based approach. In this thesis, we first assessed the risk of myocardial infarction associated with the use of oral hypoglycemics using the administrative health databases of Saskatchewan. We then evaluated the potential for residual confounding in this study by examining the distribution of unmeasured risk factors, obtained from survey data, across exposure groups. Next, we developed a simulation-based tool to study the behaviour of this bias and correct the observed exposure-outcome associations in the primary study for the impact of residual confounding. Finally, in a separate study of cholesterol lowering "statins" and diabetes progression, we addressed the issue of immortal time bias in cohort studies.

The study cohort consisted of 42,775 adults, newly treated with an antidiabetic medication. We found that among users of monotherapy, sulfonylureas were associated with a small increased risk of myocardial infarction compared with metformin (RR 1.24, 95% CI 1.06-1.45). The use of thiazolidinediones, primarily rosiglitazone, was also associated with an increased risk (RR 3.78, 95% CI 1.23-11.67) which persisted regardless of the treatment to which it was compared. We did not observe an increased risk with the use of other oral agents (RR 1.1., 95% CI 0.48-1.45).

Using data from the Canadian National Population Health Survey, we found important differences between users of sulfonylureas and metformin with regards to income, level of education, smoking status, alcohol consumption, physical activity and obesity. However, a simulation-based evaluation of these findings demonstrated that the inability to control for these unmeasured risk factors in a database study was unlikely to cause important bias for the sulfonylurea-metformin comparison. We had no information on users of thiazolidinediones.

Finally, we demonstrated that the inappropriate accounting of person-time and exposure status in the analysis of cohort studies can produce spuriously protective associations for a number of pharmacological interventions.

In conclusion, we found that the use of thiazolidinediones and sulfonylureas was associated with an increased risk of myocardial infarction. We also demonstrated the importance of correctly classifying person-time and exposure status in the analysis of cohort data.

RÉSUMÉ

Les hypoglycémiants oraux représentent le traitement de première intention dans la prise en charge du diabète de type 2. L'information concernant la sécurité de ces médicaments provient essentiellement d'essais cliniques randomisés de courte durée, à partir de populations hautement sélectionnées et de faible effectif, conçus pour détecter les changements de la glycémie. Alors, leur sécurité cardiovasculaire nécessite de ce fait de plus amples investigations à l'aide d'études observationnelles. Dans cette thèse, nous avons dans un premier temps évalué le risque d'infarctus du myocarde associé aux hypoglycémiants oraux en utilisant les bases de données administratives de Saskatchewan. Nous avons dans un second temps évalué la possibilité de biais de confusion résiduel dans notre étude, en examinant la distribution des facteurs de risque non mesurés, obtenus à partir de données d'enquête, dans les différents groupes d'exposition. Nous avons ensuite développé un outil basé sur la simulation afin d'étudier le comportement de ce biais de confusion résiduel et d'en corriger l'impact dans les associations observées entre exposition et évènement dans notre étude initiale. Enfin, dans une étude distincte portant sur les hypocholestérolémiants de type statines et la progression du diabète, nous avons abordé le problème du biais de temps immortel dans les études de cohorte.

La cohorte d'étude incluait 42 775 adultes, nouvellement traités par médicaments antidiabétiques. Parmi les patients sous monothérapie, nous avons trouvé que les sulfonylurées étaient associées à un risque légèrement augmenté d'infarctus du myocarde comparativement à la metformine (RR 1,24, IC 95% 1,06-1,45). L'utilisation des thiazolidinediones, représentées essentiellement pas la rosiglitazone, était également associée à un risque augmenté (RR 3,78, IC 95% 1,23-11,67) et quel que soit le traitement de comparaison. Nous n'avons pas observé d'augmentation de risque en rapport avec l'utilisation d'autres hypoglycémiants oraux. (RR 1,1, IC 95% 0,48-1,45).

A partir des données de l'enquête nationale sur la santé de la population canadienne, nous avons mis en évidence d'importantes différences entre les utilisateurs de

sulfonylurées et de metformine en termes de revenus, de niveau d'éducation, de tabagisme, de consommation d'alcool, d'activité physique et d'obésité. Cependant nous avons démontré, à partir d'une étude de simulation, que l'impossibilité d'ajuster sur ces facteurs de risque dans une étude de base de données n'entrainait probablement pas de biais important dans la comparaison entre sulfonylurées et metformine. Nous n'avions pas d'information sur les utilisateurs de thiazolidinediones.

Enfin, nous avons démontré qu'une prise en compte inappropriée des personnes-moments et du statut d'exposition dans l'analyse des études de cohorte pouvait produire des associations faussement protectrices pour un certain nombre d'interventions pharmacologiques.

En conclusion, nous avons mis en évidence une augmentation du risque d'infarctus du myocarde liée à l'utilisation des sulfonylurées et des thiazolidinediones. Nous avons également démontré l'importance d'une classification correcte des personnes-moments et du statut d'exposition dans l'analyse des données de cohorte.

LIST OF TABLES AND FIGURES

PREFACE

This thesis consists of eight chapters, including the introduction, literature review, methodological considerations, four manuscripts intended for publication in peer-reviewed journals, and an overall summary and conclusion. The introduction provides an overview of the population and public health burden of type 2 diabetes, particularly in the context of the cardiovascular complications of this disease, and introduces some of the methodological challenges that are encountered in the postmarketing evaluation of drug safety using an observational design, such as with the evaluation of the cardiovascular safety of oral antidiabetic medications; the primary objective of this thesis. The overview of the literature provides the background to several of the key methodological decisions taken in this thesis. This is followed by a series of three manuscripts addressing the cardiovascular safety of antidiabetic medications and bias related issues. The last manuscript re-analyzes a previously published study to demonstrate the presence of immortal time bias. The final chapter provides an overall conclusion and summary of the main results of the four manuscripts. A bibliography is presented at the end of each chapter, as well as an overall bibliography at the end of the thesis.

This thesis was prepared in accordance with the McGill University rules for a thesis by manuscript found at: http://www.mcgill.ca/gps/programs/thesis/guidelines/preparation/ and described in section I, part C.

DISCLAIMER

This thesis is based in part on non-identifiable data provided by Statistics Canada and by the Saskatchewan Department of Health. The interpretation and conclusions contained herein do not necessarily represent those of the Government of Canada, Statistics Canada, the Government of Saskatchewan, or the Saskatchewan Department of Health.

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AUTHORSHIP

This thesis presents the results of research that I initiated and developed. I wrote the study protocol related to the first manuscript which was submitted to the Canadian Institutes for Health Research. I also identified the research questions pertaining to the other three manuscripts which arose during the execution of the first project. I was responsible for obtaining the data from Saskatchewan Health, as well as for the verification and management of these data to form the study cohorts. I also conducted all of the statistical analyses required for the execution of the first project including data verification and validation and conducted the analysis for the immortal time bias project with Abbas Kezouh. The programming of the simulation study was carried out under my guidance by Sophie Dell'Aniello with assistance from Amina Barhdadi. I wrote the four thesis manuscripts. The co-authors, some of whom were members of my thesis committee, provided me with methodological and clinical advice throughout the execution of these four projects.

STATEMENT OF ORIGINALITY

This is the first study to investigate the cardiovascular safety of oral hypoglycemic agents using a design and analysis that simultaneously controlled for the potentially biasing effects of calendar time, diabetes duration, and diabetes progression and severity. This is also the first population-based study to assess the effect of sulfonylureas on the risk of myocardial infarction. To the best of my knowledge, our simulation-based study is the first to develop such a tool for the external adjustment of unmeasured confounder. Lastly, although immortal time bias has been previously described, this is the first study to identify multiple sources of immortal time and demonstrate the correlation between the degree of bias and the amount of misclassified immortal time.

CHAPTER 1: INTRODUCTION

1.1 Type 2 diabetes and cardiovascular outcomes

Diabetes Mellitus (DM) is a chronic metabolic disorder characterized by the presence of hyperglycemia due to either a deficiency in the production or secretion of insulin, diminished tissue response to the actions of insulin, or both.[1, 2] Prevalence data indicate that diabetes has reached epidemic proportions worldwide, particularly in developed countries.[3, 4] Diabetes affects approximately 3 to 6% of Canadians, although the prevalence is much higher in some ethnic groups.[5] In 2001, it is estimated that there were over two million Canadians with this disease and that an additional 1 million were expected to be diagnosed by 2015.[6] However, based on a recent Ontario study, it would appear that the estimated 2015 target has already been exceeded.[7]

The human and economic costs of diabetes are enormous. In Canada, diabetes is one of the top ten leading causes of hospitalization, the seventh leading cause of death, and one of the most common underlying cause of heart disease, stroke, kidney disease, blindness and lower limb amputations.[8] In the US, it is estimated that about 12 to 15% of total health expenditures is spent on the treatment of diabetes and its complications.[9] Although similar cost analyses are not available for Canada, in 1999 it was estimated that we spent approximately $9 billion annually on direct and indirect costs associated with this disease.[8]

Diabetes is associated with both acute and long-term complications. Acute complications include the occurrence of varying degrees of drug-induced hypoglycemia and diabetic ketoacidosis, while long-term complications include the development of micro- and macrovascular disease (ie, small and large vessel disease). Microvascular complications encompass progressive retinopathy often leading to blindness; nephropathy that may lead to renal failure; and neuropathy that often leaves individuals in chronic pain.[8] Macrovascular complications include cardiovascular disease (CVD) that significantly increases the risk of acute myocardial infarction (MI); cerebrovascular disease that manifests as fatal and non-fatal strokes; and peripheral vascular disease that may result in lower limb amputations.[8] Although both type 1 and type 2 diabetes cause similar complications, the majority of diabetes related health care expenditures is spent on

the treatment of complications in those with type 2 diabetes.[10] Indeed, the vast majority of cases of diabetes are type 2.[3, 11]

Microvascular complications are an important source of morbidity for those with type 2 diabetes but those of macrovascular origin, especially coronary artery disease, are associated with greater morbidity and mortality. Type 2 diabetes is associated with a two- to six-fold increase in the risk of CVD, and the latter accounts for 65 to 75% of all deaths in these individuals.[10, 12] Compared with the general population, those with type 2 diabetes develop CVD at a younger age, have more severe CVD, and have significantly poorer prognosis following acute cardiac events and invasive coronary procedures, even after adjusting for established CVD risk factors.[13-15] For example, at one year post-MI, 41% of diabetics will be dead, a two-fold increase compared with non-diabetics.[15] At 5-years post-MI, mortality is 72% higher than that of non-diabetics.[14, 15] The risk of re-infarction in this patient population demonstrates a similar pattern.[14] Although CVD mortality in the general populations has declined substantially over the past 30 years, the decline in those with type 2 diabetes has not been nearly as pronounced (36.4% and 13.1% among non-diabetic diabetic men respectively).[16] While the basis for these prognostic differences remains unclear, evidence is accumulating that some oral hypoglycemic agents (OHAs) may exert adverse cardiac effects.[17, 18]

Type 2 diabetes has not only reached epidemic proportions worldwide, the number of affected individuals is increasing at a much faster rate than was originally predicted. Not surprisingly, the use of oral hypoglycemic agents used to treat this disease is also increasing rapidly. Information available to date regarding the safety of these agents comes primarily from small, randomized controlled trials of highly selected populations that were powered to detect changes in plasma glucose levels (ie, HbA1c). Consequently, these trials were underpowered to address cardiovascular end points. Even meta-analyses of such studies include an exceedingly small number of cardiac events. As such, concerns regarding the cardiovascular safety of these agents warrant further study using a population-based observational approach.

1.2 Pharmacoepidemiologic studies

Observational studies have made significant contributions to our understanding of the risks and benefits associated with drug therapy. Indeed, pharmacoepidemiologic studies have often been the first to identify or confirm the presence of important adverse health outcomes associated with the use of medications, as seen recently with the adverse cardiac effects of the cyclooxygenase-2 (COX-2) inhibitors[19, 20] and ergot-derived dopamine agonists[21]. These studies have also been instrumental in addressing aspects of drug safety and effectiveness that cannot be readily or adequately evaluated using an experimental design. For example, the time-varying nature of the risk[22] and the health benefits of drugs for important but rare outcomes[23, 24]. As such, pharmacoepidemiologic studies are needed to compliment the information provided by randomized controlled trials.

Increasingly, pharmacoepidemiologic studies are conducted using electronic, administrative health databases. The large size and unselected nature of the populations captured by these databases provide results that are both precise and generalizable to persons who require treatment in routine practice, and are sufficiently powered to assess uncommon but important adverse health outcomes. These populations can also be followed for extended periods of time in a cost and time efficient manner.[25] In contrast, the highly selected populations of randomized controlled trials are typically younger and healthier than those treated in practice owing to the exclusion of common comorbidities and the use of concomitant drugs. Furthermore, clinical trials are typically powered to assess drug effectiveness and are, therefore, underpowered to detect differences in important but less common adverse health events. Even when data from meta-analyses are available, these estimates do not necessarily reflect the adverse event experience of the populations treated in routine practice. Despite some important advantages, pharmacoepidemiologic database studies have been the source of considerable controversy, in part due to their limited ability to control some potential sources of bias. Indication bias, or confounding by indication, is an example of this.

Administrative health databases typically lack information on some important determinants of health outcomes including socio-economic status, health and lifestyle factors such as self-perceived health status, alcohol consumption, smoking status, body mass index (BMI), and physical activity. When one or more of these factors influences a physician's choice of treatment, that factor becomes independently associated with both the risk of the outcome and the probability of being exposed and as such, introduces confounding by indication bias.[26] Indeed, the possibility of residual confounding due to unmeasured risk factors can be the most important threat to the validity of pharmacoepidemiologic studies. The association between the use of oral hypoglycemic agents (OHAs) and the risk of acute myocardial infarction (MI) is an example of this. Metformin, one of the commonly prescribed OHAs, may be preferentially prescribed to obese individuals because of its mechanism of action and well established efficacy in this population. However, obesity is also an important determinant of MI risk and information on body mass index (BMI) is typically unavailable in administrative health databases. As such, pharmacoepidemiologic studies of OHAs and MI risk need to use additional methods to assess and correct the results for the possibility of residual confounding.

Immortal time bias is another important threat to the validity of pharmacoepidemiologic studies and this bias is being observed with increasing frequency in cohort studies.[27] While immortal time bias is not as well recognized as confounding by indication, it nonetheless has the potential to negatively impact clinical practice and thus, population health. Several recent example of immortal time bias are found in studies of pharmacological interventions for type 2 diabetes. This bias, which arises from the inappropriate handling of follow-up time and exposure status, requires careful consideration when analyzing cohort data.

1.3 Rationale and objectives

In this thesis we focused on the use of observational methodology, particularly cohort studies, to assess the cardiovascular safety of oral hypoglycemic agents, and address bias related issues in the postmarketing evaluation of drug safety. Specifically, we addressed confounding due to several dimensions of time including diabetes duration

(pre- and post-treatment initiation), diabetes progression and severity, and calendar time, as well as residual confounding due to unmeasured risk factors and immortal time bias.

The primary objectives of this thesis were to address the long standing controversy regarding the potentially negative cardiac effects of the sulfonylureas, the most commonly prescribed oral antidiabetic agent, and identify factors that modified this risk. Specifically, we evaluated the risk of acute MI associated with current exposure to these agents. In view of the recent controversy regarding the possibility of a similar risk with the use of thiazolidinediones, the newest class of antidiabetic medications, we also assessed this risk in association with the current use of these agents. These two objectives, addressed in the first manuscript, comprised what is referred to in this thesis as the "main study". Secondarily, we assessed whether the conditions for indication bias were met in the main study and then quantify and correct for the presence of residual confounding once this possibility had been established. Finally in a separate study, we assessed whether and to what extent immortal time bias accounted for a previously reported protective association between the use of cholesterol lowering "statins" and the need to initiate insulin therapy in type 2 diabetes.

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CHAPTER 2: REVIEW OF THE LITERATURE

2.1 Diagnosis and classification of diabetes

The diagnostic criteria for diabetes, as well as the classification of this disease, have changed considerably since the 1980s. The most significant changes that have taken place with regards to the diagnosis of diabetes include the type of test used to make the diagnosis (i.e., fasting plasma glucose levels versus 2-hour post glucose tolerance test) and a lowering of the diagnostic threshold for the fasting plasma glucose (FPG) test to a level that correlates more closely with the development of microvascular complications.[1-6] These changes mean that individuals diagnosed more recently may initially be at an earlier stage of diabetes than those diagnosed prior to these practice changes and as such, may initially be at lower risk of diabetes related complications including acute MI. Moreover, treatment recommendations have also changed over the past two decades. The implication of these changes is that calendar time may be associated with the risk of MI.

The current approach to classifying diabetes is based on the etiology of this disease rather than on its treatment and includes four categories; (i) type 1 diabetes, (ii) type 2 diabetes, (iii) gestational diabetes, and (iv) 'other specific types' of diabetes.[2, 7, 8] Type 1 diabetes, formally known as 'insulin dependent diabetes mellitus' (IDDM) or juvenile onset diabetes, is characterized by pancreatic beta cell destruction (either autoimmune or idiopathic) and the subsequent inability to produce insulin.[2, 9, 10] Type 1 diabetes is typically diagnosed in childhood or adolescence. 'Latent Autoimmune Diabetes in Adults' (LADA) is a latent form of type 1 diabetes that is present in approximately 6 to 10% of adults over the age of 25 years with diabetes.[2, 11] Although LADA can initially be misdiagnosed as type 2 diabetes given its presentation in adults, individuals affected by this form of diabetes are typically younger than those with frank type 2 disease.[11] Type 2 diabetes, previously classified as 'non-insulin dependent diabetes' (NIDDM) or adult-onset diabetes, is characterized by insulin resistance (ie, diminished tissue response to the actions of *endogenous* insulin) and abnormal insulin secretion from the pancreas (ie, beta cell failure), either of which may predominate in a given individual.[12, 13] This type of diabetes usually occurs after age 30 and depending on the population studied, the mean age at diagnosis is often well into the sixth decade.[2, 8-10, 14, 15] Consequently, one of the characteristic that generally distinguishes type 2 from type

1 disease is age at diagnosis. The methodological implication is that the use of an older age cut point to identify a cohort of individuals with type 2 diabetes will minimize the potential for including type 1 disease. Although type 2 diabetes is increasingly being diagnosed in obese children and adolescents, older age at treatment initiation is more likely to represent type 2 diabetes, particularly during the 1980s and 1990s. Type 2 diabetes is the predominant clinical manifestation of this disease and accounts for more than 90% of all cases.[9, 10, 13, 16, 17] Gestational diabetes mellitus is characterized by the onset or recognition of glucose intolerance during pregnancy, while 'other specific types' includes diabetes secondary to genetic defects, endocrine disorders, infections and drugs.[2, 8]

2.2 Treatment of diabetes

The treatment of diabetes is also determined by its etiology.[2, 3] Those with type 1 diabetes are unable to produce insulin and consequently require the administration of *exogenous* insulin to survive. In contrast, individuals with the latent form of type 1 (LADA) often have residual islet cell function at the time of diagnosis and may not require exogenous insulin right away. However, these individuals eventually require insulin injections, and much sooner than persons with type 2 disease. In contrast, individuals with type 2 disease have functioning pancreatic islet cells at the time of diagnosis. Consequently, type 2 diabetes does not initially require insulin to control hyperglycemia and may be managed with diet and exercise. When lifestyle modifications fail to control hyperglycemia, an oral hypoglycemic agent (OHA) that either stimulates the pancreas to release insulin (sulfonylureas or meglitinide) or one that improves peripheral tissue sensitivity to the effects of *endogenous* insulin (metformin or thiazolidinediones) is initiated. Because type 2 diabetes is a progressive disease that is characterized by an ongoing deterioration of beta-cell function and a corresponding loss of glycemic control over time, regardless of the treatment chosen or treatment intensity,[11, 18] many individuals go on to require the addition of a second oral agent and eventually, *exogenous* insulin to maintain good glycemic control.[11, 18-21] Consequently, the management of type 2 diabetes often follows a stepwise approach from monotherapy using an oral hypoglycemic, to combined therapy using two or more oral agents or a

combination of oral therapy and insulin, to insulin monotherapy. In this way, the treatment received by an individual is correlated with diabetes progression or severity. The implication of this in an observational study is that stratifying the analysis by treatment intensity can control, at least in part, for diabetes progression and severity.

Treatment recommendations for the management of type 2 diabetes have changed over time. The most significant of these changes include the lowering of target glucose levels for glycemic control, the corresponding use of more intensive therapy, the choice of agent for initial therapy, and the increasing use of polypharmacy to achieve glycemic targets. For example, prior to 2003, the recommended treatment of type 2 diabetes was the stepwise approach previously described, however, in 2003, the Canadian practice guidelines were changed to advocate the early use of combination therapy as a viable treatment option. Furthermore, metformin is now preferred over sulfonylureas in obese individuals. The implications of these changes are that the probability of being exposed to a particular treatment regimen could be associated with calendar time. Since calendar time may be associated with both the risk of MI and the probability of being exposed to a specific treatment, the potentially biasing effect of calendar time therefore needs to be accounted for in the design and/or analysis of observational studies of antidiabetic medications and cardiovascular outcomes.

2.3 Choice of anti-hyperglycemic agent

There are four categories of anti-hyperglycemic agents, representing six drug classes, currently available in Canada (Table 2.1).[22] Insulin, which is given by injection, is used by all individuals diagnosed with type 1 diabetes as well as some with type 2 disease, while OHAs are only indicated for the management of type 2 diabetes. Although the oral agents differ with regards to their mechanism and duration of action, indications, and contraindications, they have similar effects on glycemic control, lipids, and other intermediate end points.[11, 22, 23] Indeed, a recent systematic review of randomized controlled trials concluded that most oral agents including metformin, repaglinide and thiazolidinediones, improved glycemic control to the same degree as sulfonylureas (absolute decrease of about 1% in hemoglobin A1c ($HbA1_C$) level).[24] Thus, efficacy

should not be an important determinant of treatment choice. As well, under a universal drug insurance program, the cost of the treatment should not influence a physician's choice. There are differences in tolerability between the oral agents. For example, sulfonylureas and repaglinide are more likely to cause hypoglycemia, thiazolidinediones carry a higher risk of congestive heart failure, and metformin is associated with a high incidence of gastrointestinal side effects (flatus, nausea, vomiting, and abdominal pain). As such, individual agents may be avoided on the basis of these side effects. In theory, metformin may be prescribed as first choice since it is associated with less weight gain than thiazolidinediones (TZDs) and a lower incidence of hypoglycemia than sulfonylureas.[2, 11, 24] In addition, metformin is considered the drug of first choice in overweight persons, except in the presence of hepatic or renal failure, in which case sulfonylureas are preferred.[2, 25] Despite these recommendations, prescribing data indicate that the vast majority of individuals with type 2 diabetes are initially treated with a sulfonylurea eventhough 60% of persons with this disease are obese.[26,28] It is therefore not surprising that there is evidence to suggest that weight and body mass index (BMI) are only weakly associated with treatment choice.[26-29] For example, in a prospective cohort study of 2,275 individuals with type 2 diabetes, the mean (±SD) baseline weight for persons prescribed metformin compared to glyburide (a sulfonylurea) was 77 kg (±13) vs 81 kg (±17), and mean BMI (±SD) was 27 (± 4) kg/m^2 vs 29 (±5) kg/m^2.[27] On the other hand, prescribing restrictions imposed by provincial drug formulary policies may introduce some channeling bias. Given the higher cost and lack of efficacy advantage of TZDs and repaglinide, some provincial drug plans, including Saskatchewan Health, restrict the use of these agents to individuals who are intolerant, have a contraindication, or are deemed uncontrolled on a sulfonylurea or metformin. The influence of these restrictions on the magnitude and directions of the risk estimates need to be taken into account in the interpretation of study results.

The choice of treatment for combination therapy is complicated by the number of individual agents available and important variations across physicians' practices with regards to choice of agents to combine and the sequence in which they are prescribed.[30] It is usually recommended that a second oral agent from a different class be added once the

original treatment fails to control hyperglycemia (i.e., as beta-cell deterioration progresses). However, some physicians may choose to introduce insulin sooner, depending on their perception of the person's compliance and tolerance.[30] The implication is that identifying an appropriate treatment comparator for combination therapy is considerably more challenging. Moreover, since insulin monotherapy is often the treatment of last resort there is no appropriate comparator treatment.

Physicians' prescribing choices ought to reflect the recommendations of published practice guidelines whenever these are available. However, not only does prior research suggest that many physicians do not conform to these recommendations, [31] those that do still face a variety of treatment options. As such, it is likely that the choice of an anti-hyperglycemic treatment is driven by patient factors (clinical and behavioural), physician-specific preferences, marketing pressures, and a number of other factors such as cultural and geographic. The benefit for researchers is that this introduces an important amount of random variation with regards to prescribing decisions. Furthermore, a recent study evaluating the determinants for prescribing a cyclooxygenase-2 (COX-2) inhibitor preferentially over a nonsteroidal antiinflammatory drug (NSAID) found that physician preference was a much stronger predictor of treatment choice than were patient characteristics.[32]

2.4 Type 2 diabetes and macrovascular disease

The onset of type 2 diabetes is, for the most part, insidious.[33] As there are few obvious symptoms initially, up to 7 to 12 years can elapse before a clinical diagnosis is made.[34] Consequently, even newly diagnosed cases of type 2 diabetes represent prevalent disease. This implies that clinically relevant morbidity may be present at the time of diagnosis. Indeed, up to one-third of newly diagnosed cases of type 2 diabetes may present with one or more diabetes related complication, often macrovascular in origin, which has been shown to be an important determinant of diabetes related mortality.[11, 35] Since mortality is also known to increase with duration of diabetes, [36] the presence of such complications at diagnosis is an important marker of diabetes progression or severity and, of poorer prognosis.[35, 37-40] As such, observational studies of OHAs and MI risk need

to account for diabetes duration and the presence of related complications to minimize the potential for confounding by disease progression and severity.

Although microvascular disease is an important source of morbidity for persons with type 2 diabetes, macrovascular disease is associated with greater morbidity and mortality. [41] Macrovascular complications occur at least twice as often as microvascular ones and are the most common cause of death in this population; accounting for up to 75% of all deaths.[36, 41-43] Macrovascular morbidity manifests itself predominantly as coronary heart disease.[11] The primary risk factors for the development of cardiovascular (CV) events in those with type 2 diabetes are, for the most part, the same as those for individuals without diabetes and include age, sex, hypertension, smoking, dyslipidemia, and obesity.[39, 44, 45] However, recent evidence from the UKPDS [46] and the Diabetes Intervention study [39, 47] suggests that obesity may not be an independent predictor of CV events once the presence of diabetes has been accounted for. Other potentially important independent predictors of cardiovascular disease (CVD) that are specific to persons with type 2 diabetes include the presence of albuminuria at diagnosis (a marker for nephropathy and hence disease progression), [44, 45] history of any diabetes-related complications,[35] and duration of diabetes [36].

Clinical evidence to date indicates that the degree of hyperglycemia (ie, lack of glycemic control) in those with type 2 diabetes is strongly correlated with the development and severity of *microvascular* complications.[11, 48, 49] Indeed, the UKPDS trial has demonstrated that targeting lower levels of HbA1c slows the development and progression of microvascular complications. [46] However, the exact nature of the relationship between hyperglycemia and *macrovascular* disease has yet to be fully elucidated. Observational studies investigating this relationship in individuals with type 2 diabetes have yielded conflicting results. Of five cross-sectional studies published to date, [50-54] only one reported a positive, independent association between glycemic control (measured using HbA1c levels) and macrovascular disease [50]. However, cross-sectional studies are limited by their inability to establish temporality between hyperglycemia and the incidence of CVD, [55] the possible effect of survival bias,[55] and the influence of current

exposure to anti-diabetic drugs on measures of hyperglycemia. The contribution of hyperglycemia to the development of CVD is no clearer when assessed using a prospective design. Of eight such studies,[56-63] two reported no independent association,[62, 63] and another reported a significant association that disappeared after adjusting for lipoprotein levels[59]. The remaining five studies reported a small but significant association with either CVD incidence or mortality [56-58, 60, 61] but two of these studies failed to take into account the independent contribution dyslipidemia,[56, 58] one did not include smoking status,[56] and the results of another are uncertain since well established CVD risk factors such as hypertension and dyslipidemia were not found to be independent predictors of CVD in the population studied [57]. The UKPDS, a large intervention study reported a small but non-significant association between glycemic control and MI (RR 0.84, 95% CI 0.71-1.00), no association with stroke (RR, 1.11, 95% CI 0.81-1.51), diabetes-related mortality (RR 0.90, 95% CI 0.73-1.11), and all-cause mortality (RR 0.94, 95% CI 0.80-1.10).[11] These data indicate that the degree of hyperglycemia is unlikely to be a major determinant of CVD outcomes once well established risk factors have been taken into account, however, this is a source of considerable controversy. What is known at the present time is that, unlike the prevention of microvascular complications where there is clear evidence that better control of hyperglycemia reduces the incidence and progression of microvascular complications, there is no clear evidence that better control of hyperglycemia reduces the incidence of macrovascular disease.[42, 64]

2.5 Cardiovascular effects of oral hypoglycemics

It is now well established that diabetes itself is bad for the heart but there is also evidence to suggest that, independent of their effect on glycemic control, some classes of oral hypoglycemics may exert cardiotoxic effects, while others may offer cardioprotective benefits.

2.5.1 Sulfonylureas

The sulfonylureas are the most frequently prescribed drugs for the treatment of type 2 diabetes, with as many as 75 to 80% of individuals initially treated with one of

these agents.[28, 29, 65] Although they have been available since the early 1970's, it wasn't until the mid- to late-1990's that it was discovered that sulfonylureas stimulated the release of insulin from the pancreas by binding to the "sulfonylurea receptor" and *closing* adenosine triphosphate-sensitive potassium (K_{APT}) channels on the beta cells of the pancreatic islets.[66-68] However, sulfonylureas may also exert extra-pancreatic effects due to the presence of K_{ATP} channels in other tissues of the body.

The K_{ATP} channel was first identified in the mid- to late 1980s and subsequently shown to be composed of two subunits: the sulfonylurea receptor (SUR) and the potassium (K+) ion channel.[69-72] These ion channel complexes were found to be present in the plasma membrane of the pancreatic beta cells, cardiac muscle, vascular smooth muscle, and neurons (Table 2.2).[67, 73-75] To date, three subtypes of the SUR/ K_{ATP} channel complex have been identified: SUR1 (found in pancreatic beta cells and neuronal cells), SUR2 (found in cardiac and skeletal muscle cells), and SUR2B (found in vascular smooth muscle cells).[71, 72, 76] By the mid- to late 1990s, it became clear that several endogenous cardioprotective mechanisms, referred to as "ischemic preconditioning" (IPC), were mediated through the *opening* of the K_{ATP} channels located in the myocardium and vascular smooth muscle.[67, 73-75, 77] For example, in myocardial cells, the *opening* of the K_{ATP} channels during experimentally induced ischemia was shown to decrease myocardial contraction, reduce cellular oxygen demand, and significantly reduce infarct size.[78] In vascular smooth muscle cells, the *opening* of these channels was shown to lead to a reduction in vascular resistance and a beneficial increase in blood flow.[79] Thus, the "preconditioned" myocardium appears to be less vulnerable to the potentially detrimental effects of subsequent ischemic injury including myocardial ischemia. Although most of these experiments were conducted in animal models, there is now unequivocal evidence that IPC occurs in humans as well.[80, 81] For example, several investigators have reported that using repeated episodes of induced ischemia during angioplasty resulted in clinically significant improvements of indicators of ischemia severity and tissue injury including intensity of ischemic pain, extent of ST segment changes, severity of wall abnormalities, peak creatinine kinase (CK) levels, and myocardial lactate production.[82-86] Similar findings were observed following exercise-induced ischemia[87, 88] and surgery-induced

ischemia[89-91]. In addition, both short-term and long-term clinical benefits have been demonstrated in studies evaluating the effect of preinfarction angina, a state known to induce ICP, among individuals suffering an acute MI. In a retrospective analysis of the TIMI-4 trial, Kloner et al. [92] found that the presence of angina any time preceding the infarct was associated with smaller infarct size, reduced incidence of cardiogenic shock and congestive heart failure, and lower in-hospital mortality. Moreover, individuals who experience angina within 24 hours of their acute infarction appear to have a lower risk of life-threatening ventricular arrhythmias associated with reperfusion [93, 94] and higher 1- and 5-year survival [93, 95].

During the same time period, evidence began to accumulate suggesting that sulfonylureas were capable of antagonizing the beneficial cardiac effects of IPC and worsening the extent of tissue damage during myoccardial ischemia or infarction.[67, 96, 97] For example, glyburide was shown to inhibit coronary vasodilatation in isolated guinea-pig hearts,[98] reduce coronary blood flow in unanaesthesized dogs,[99] increase coronary vascular resistance resulting in myocardial ischemia in dog and rabbit hearts,[100] aggravate ischemic injury and increase infarct size in several animal models,[78, 101-103] impair the recovery of myocardial contractile function in humans atrial tissue,[104] and decrease left ventricular ejection fraction (LVEF) following drug-induced ischemia [105]. In addition, *in-vitro* studies also demonstrated that sulfonylureas were capable of blocking the beneficial effects of several K_{ATP} channel *opening* drugs, some of which are currently used in clinical practice.[106, 107] Paradoxically, sulfonylureas also exert beneficial effects on the cardiovascular system. For example, glyburide and glipizide have been shown to inhibit reentrant arrhythmias associated with myocardial ischemia or infarction and as such, could decrease the risk of sudden cardiac death.[73, 74, 99, 108-110] Sulfonylureas also increase the production of tissue plasminogen activator (TPA) by endothelial cells, inhibit platelet function, and decrease serum triglycerides.[73, 111] However, it is unclear whether sulfonylureas are likely to exert any effect on the cardiovascular K_{ATP} channels at concentrations achieved with usual therapeutic doses.[67, 73-75, 106]

The first evidence of the clinical relevance of the potentially cardiotoxic effects of sulfonylureas came from the University Group Diabetes Program (UGDP) study published in 1970 (Table 2.3).[112] This intervention trial of 1027 individuals newly diagnosed with type 2 diabetes was designed to compare the efficacy of oral hypoglycemics, insulin and diet alone in the prevention of diabetes-related vascular complications. The authors reported an increase in cardiovascular mortality of approximately 1% per year in those receiving tolbutamide (a sulfonylurea) compared to diet alone. At the time, these results were dismissed as paradoxical, in part due to the lack of a physiological basis for this unexpected finding. This study was also extensively criticized because of methodological and statistical shortcomings.[113-115] For example, the control group was found to have a skewed sex distribution that may have resulted in a spuriously low cardiovascular mortality for this group and biased the comparisons with the active treatment groups. A number of smaller studies of various designs were subsequently published through the 1970s and 80s, and while several of these supported the findings of the UGDP trial,[116-123] others did not[124-127]. In addition, since most of these studies involved the use of tolbutamide, their findings cannot necessarily be extrapolated to other sulfonylureas currently used in practice.

Two additional randomized intervention trials have assessed the association between sulfonylureas and cardiovascular morbidity and mortality: The Veterans Affairs Cooperative Study[128] and the United Kingdom Prospective Diabetes Study (UKPDS) [11]. In the veterans study, 153 men with prevalent type 2 diabetes were followed for a mean of 27 months to compare the effect of insulin monotherapy, insulin combined with a sulfonylurea (glypizide), and titrated doses of insulin on the development of new cardiovascular events and cardiovascular mortality.[128] This study found neither beneficial nor detrimental effects for sulfonylureas compared with insulin. As this was a feasibility trial, it lacked power to detect true differences between treatments and as such, its results are inconclusive. The UKPDS, the largest and longest intervention trial of type 2 diabetes, randomized 4209 newly diagnosed individuals to either “intensive” treatment using either a sulfonylurea (chlorpropamide, glyburide, or glipizide based on physician’s choice), metformin (a biguanide) in overweight persons, or insulin monotherapy to maintain

fasting plasma glucose (FPG) at < 6 mmol/L, or to "conventional" treatment using diet to maintain FPG below 15 mmol/L.[11, 25] Both treatment arms permitted stepwise additions of an hypoglymemic, followed by insulin, to maintain plasma glucose as close to target levels as possible. Of the 1,573 subjects who were randomized to begin therapy with a sulfonylurea, 50% received chlorpropamide, 39% glyburide, and 11% glipizide. The results demonstrated that tight glycemic control with a sulfonylurea, metformin, a combination of these two, or either one combined with insulin, significantly reduced microvascular complications but not macrovascular ones.[11] In addition, no differences in outcomes were observed across the various sulfonylureas. In the overweight group, compared with individuals assigned to "conventional" therapy, those on "intensive" therapy using metformin monotherapy had 32% (95% CI, 13-47%) fewer diabetes-related outcomes, 42% (95% CI, 9-63%) fewer diabetes-related deaths, and 36% (95% CI, 9-55%) lower all cause-mortality.[25] In contrast, a large and statistically significant increase in diabetes-related deaths (HR 1.95; 95% CI, 1.02-2.75) and all-cause mortality (HR 1.60; 95% CI, 1.02-2.52) was observed for those allocated to "intensive" treatment using a combination of a sulfonylurea and metformin compared to "conventional" treatment. Although the latter results have been dismissed by some as chance findings (i.e., type I error), [129] they are nonetheless worrisome given the high prevalence of use of these two oral agents and the beneficial effects demonstrated for metformin monotherapy.

Since the release of the UKPDS results, seven observational studies evaluating the cardiovascular effects of sulfonylureas have been published: five were retrospective cohort studies [130-134] and two were prospective cohorts [27, 135] (Table 2.4). Five of these evaluated post-MI death associated with the use of sulfonylureas, [27, 130, 131, 133, 135] one cardiac deaths, [132] and the other all-cause mortality [134]. The results of these studies are conflicting. Four reported no increased risk of death with sulfonylureas,[27, 131, 133, 135] while the other three did [130, 132, 134]. With the exception of Johnson et al., [134] all of the others evaluated prevalent diabetes, prevalent exposure, and used comparator groups that did not control for confounding by diabetes duration, progression, and severity. For example, Garratt et al [130] examined the effect of sulfonylureas on cardiovascular mortality among 185 persons with type 2 diabetes undergoing direct coronary angioplasty for acute

myocardial infarction. Early mortality in users of sulfonylureas was more than twice that of non-users of sulfonylureas (OR 2.53, 95% CI 1.13-5.67). However, the comparator group in this study included individuals who were controlled by diet alone as well as users of insulin. Such a heterogeneous reference group makes it difficult to assess the true cardiac effect of sulfonylureas. In addition, these investigators did not control for duration of disease and calendar time. Olsson et al [132] reported similar results for overall mortality (OR 1.63, 95% CI 1.27-2.09) using a population-based retrospective cohort approach. However, in this study the comparison was made between combined oral therapy (i.e., a sulfonylurea and metformin) and sulfonylurea monotherapy. Since the exposure group of interest represented individuals at higher risk of diabetes-related death by virtue of requiring combination therapy, and both groups included users of sulfonylureas, these results likely reflect the influence of disease severity or progression rather than the cardiac effects of sulfonylureas. The study by Fisman et al [27] compared mortality rates associated with the use of glyburide (a sulfonylurea) or metformin monotherapy and combined oral therapy with those of individuals controlled by diet therapy. After a mean follow-up of 7.7 (±1.5) years, all-cause mortality was similar for monotherapy using either glyburide or metformin (HR 1.22, 95% CI 1.02-1.96 and HR 1.26, 95% CI 0.81-1.96, respectively) but higher for users of combined therapy (HR 1.53, 95% 1.20-1.96). These results are also likely confounded by disease severity and progression. Johnson et al., [134] is the only observational study published to date that used a design and analysis that controlled for the sources of bias previously mentioned. Unfortunately, this study is biased by inappropriately accounted for immortal time.

2.5.2 Metformin

As previously discussed, the results of the UKPDS study showed that metformin exerted beneficial effects on diabetes-related deaths and all-cause mortality when used alone but not when combined with a sulfonylurea. [25] Although these findings originally raised some concerns about the cardiac safety of metformin, these results have not been substantiated by other studies. Moreover, these findings could be attributabed to the potentially detrimental effects of sulfonylureas.

2.5.3 Thiazolidinediones

The thiazolidinediones (TZDs) are the newest class of oral antidiabetic medications available for the treatment of type 2 diabetes. The first of these agents, troglitazone, was removed from the market shortly after its approval because of serious liver toxicity. Two other TZDs, pioglitazone and rosiglitazone, introduced in 1999 remain on the market. [136, 137] TZDs are selective agonists of peroxisome proliferator-activated receptor-gamma (PPAR-gamma). [138] These receptors play an important role in the regulation of lipid and glucose metabolism and explain the beneficial effects of these agents on lipid and glucose levels. However, PPARs are also expressed in a wide variety of tissues where they turn on and off a large number of genes, the function of most of which are unknown.

The vast majority of TZD trials published to date for pioglitazone and rosiglitazone have primarily evaluated surrogate end points including glycemic control, lipids, blood pressure, and weight.[139] TZDs appear to exert beneficial effect on high-density lipoprotein (HDL) cholesterol levels but harmful effect on low-density lipoprotein (LDL).[24] A potentially important difference between the two TZDs is that pioglitazone has been found to decrease triglyceride levels, while rosiglitazone increases them. The clinical significance of these differences is unknown as there are no head-to-head trials of these two agents evaluating cardiovascular outcomes. Only one TZD trial to date has specifically evaluated cardiovascular end points. The PROspective pioglitazone Clinical Trial in macrovascular Events (PROactive) study randomized 5,238 persons with type 2 diabetes and evidence of macrovascular disease to pioglitazone (15 to 45mg per day) or placebo in addition to their current glucose-lowering treatments.[140] After a mean of 34.5 months, there was a trend toward a benefit for pioglitazone for the primary composite end point of all-cause mortality, nonfatal MI, stroke, acute coronary syndrome, endovascular or surgical intervention on the coronary or leg arteries, or amputation above the ankle (HR 0.90, 95% CI 0.80-1.02). However, pioglitazone was found to significantly reduce the occurrence of the secondary end point (HR 0.84, 95% CI 0.72-0.98) but it is not clear if this was a prespecified analysis. Users of pioglitazone had significantly more edema and heart failure but these events were not included as cardiovascular end points. Two

meta-analyses of pioglitazone have also been published with one concluding that this agent was associated with a significantly lower risk of death, MI, and stroke (HR 0.82, 95% CI 0.72-0.94), [141] and the other reporting no definitive evidence of a benefit for hard clinical end points [142].

Four meta-analyses have evaluated the cardiac safety of rosiglitazone. [143-146] Three reported that rosiglitazone significantly increased the risk of acute MI by approximately 40%, [143, 144, 146] while the fourth, a re-analysis of one of these using a different statistical technique, concluded that the risk of MI and cardiac death was uncertain [145]. An unplanned interim analysis of the Rosiglitazone Evaluated for Cardiovascular Outcomes (RECORD) study has also been published.[147] This open-label, unblinded randomization, non-inferiority study found no increased risk for the primary end point of hospitalization or cardiac death, adjudicated and non-adjudicated events, (HR 1.11, 95% CI 0.93-1.32). However, despite a lack of power, the upper limit of the 95% confidence interval surpassed the study's non-inferiority threshold. Moreover, the choice of the non-specific end point of hospitalization may have introduced enough non-differential misclassification as to bias the results towards the null (ie, in favour of non-inferiority).

2.6 Limitations of research to date

The most important limitation of intervention trials of sulfonylureas published to date is that they have failed to provide a definitive answer regarding the potential cardiotoxicity of these agents. Although the UKPDS is the largest and longest trial published to date, it is not without limitations. Overall, the UKPDS was quite large but the size of the various treatment groups analyzed was small from the perspective of evaluating adverse drug effects. For example, a total of 4,209 subjects were randomized but the analyses of aggregate and individual end points were based on groups ranging in size from 342 for metformin to 911 for insulin.[11, 148] Of greater concern regarding the detection of possible cardiotoxicity, the analyses were conducted on an intent-to-treat basis. The stepwise addition of drugs to randomized treatments, necessitated by the progressive nature of this disease, resulted in substantial overlap in exposure across pre-defined (intent-to-treat) comparison groups. This "mixing" of drug treatment, which

caused significant misclassification of exposure when the intent-to-treat analyses were performed, likely biased the rate ratios towards the null and obscured any true differences between these agents, if one existed. It is noteworthy that the "as exposed" analysis conducted for the adverse effect of hypoglycemia yielded a higher estimate than that of the intent-to-treat analysis. Despite assurances to the contrary, the UKPDS study (which did not observe a beneficial effect on macrovascular end points as expected) did not rule out the possibility that sulfonylureas may exert negative cardiac effects. In fact, cardiotoxicity could explain the lack of apparent cardiovascular benefit observed in this study.

Trials evaluating the thiazolidinediones had similar limitations. Most of these were powered to detect benefits in glycemic control, a surrogate end point, and as such lacked power to assess hard cardiovascular outcomes. In addition, the vast majority of these trials were of short duration and many excluded persons at high risk of cardiovascular morbidity or mortality. Although two recent meta-analyses of rosiglitazone reported a significantly increased risk of MI, these results require confirmation using a population-based approach given that the populations studied in these trials were much younger and healthier than the vast majority of individuals treated in routine practice.

Observational studies published to date evaluating the cardiac effects of sulfonylureas share similar methodological shortcomings. The results of these studies are likely confounded by diabetes progression and severity, by duration of diabetes, and by calendar time (i.e., time trends). For example, most studies have either not adjusted for diabetes progression and severity and duration of diabetes, or have adjusted for one only one of these two important determinants of cardiovascular events. As previously discussed, as diabetes progresses, individuals' requirements change from oral monotherapy (either a sulfonylurea or a biguanide), to combination therapy (both oral drugs combined or either agent combined with insulin), and finally to insulin monotherapy. In other words, the therapy to which an individual is exposed is, to a certain extent, a proxy for disease progression and severity. As such, studies comparing

cardiovascular outcomes for monotherapy to that of combination therapy or insulin monotherapy may be inherently biased. Confounding by calendar time is another important source of bias in these studies given that the diagnostic criteria, classification, and treatment of type 2 diabetes have changed considerably in the last few decades. Consequently, an individual diagnosed and treated in the 1990s may represent a very different risk profile for the study outcomes than one diagnosed and treated at an earlier time and also have differing probabilities of exposure to specific agents and regimens. Of the studies reviewed, only Olsson et al[132] controlled for the confounding effects of calendar time. Unfortunately these investigators failed to control for diabetes duration and progression.

2.7 Conclusion

Based on the evidence available to date, it is unclear whether the use of sulfonylureas and thiazolidinediones contribute to the disproportionately increased rate of cardiovascular morbidity and mortality observed in persons with type 2 diabetes. However, given the increasing prevalence of type 2 diabetes, the routine use of oral hypoglycemics in this population, the high baseline risk of macrovascular disease, and the significant degree of uncertainty that exists regarding the cardiac safety of oral hypoglycemics, there is a need for further studies using a population-based cohort approach to reflect the use of these medications in routine practice.

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Table 2.1 Classification, mechanism of action, indications and contraindications of anti-hyperglycemics available in Canada

Category	Drug class	Mechanism of action	Indications	Contraindications
Insulins				
Insulins	Insulins	Exogenous insulin – regulates glucose metabolism	• Primary treatment of type 1 diabetes • Gestational diabetes • Post-pancreatectomy diabetes • Treatment of diabetic ketoacidosis • Hyperglycemic, nonketotic coma • In type 2 diabetes uncontrolled by diet and oral hypoglycemic agents	• During periods of hypoglycemia • Previous hypersensitivity reaction
Oral Hypoglycemic Agents (OHAs)				
Secretagogues	Sulfonylureas (chlorpropamide, gliclazide, glimepiride, glyburide, tolbutamide)	Adenosine triphospate-sensitive potassium channels (K_{ATP}) on the beta cells of the pancreatic islets. Stimulate the release of insulin from the pancreas by binding to the "sulfonylurea receptor" and closing K_{ATP} channels (i.e., K_{ATP} channels antagonists)	• Type 2 DM in those uncontrolled by lifestyle modifications, alone or in combination with metformin	• Type 1 DM • Pregnancy and lactation • Previous hypersensitivity reaction
	Meglitinides (nateglinide, repaglinide)	As for sulfonylureas	• Type 2 DM in those uncontrolled by lifestyle modifications, alone or in combination with metformin	• Type 1 DM • Previous hypersensitivity reaction • Diabetic ketoacidosis
Insulin sensitizers	Biguanides (metformin)	Mode of action has not yet been fully elucidated. It is believed to potentiate the effects of endogenous insulin, particularly at peripheral sites	• Type 2 DM in those uncontrolled by lifestyle modifications • May be of value in obese diabetic patients	• Type 1 DM • Previous hypersensitivity reaction • Diabetic ketoacidosis • Renal or hepatic failure
	Thiazolidinediones (pioglitazone, rosiglitazone)	PPAR-gamma agonists – depends on the presence of endogenous insulin; decreases insulin resistance and reduces circulating levels of insulin	• Type 2 DM in those uncontrolled by lifestyle modifications, alone or in combination with a sulfonylurea or metformin	• Previous hypersensitivity reaction • Serious hepatic impairment • Acute heart failure
Other anti-hyperglycemics	Alpha –glucosidase inhibitors	Acarbose – delays the digestion of ingested carbohydrates	• Type 2 DM in those uncontrolled by lifestyle modifications	• Diabetic ketoacidosis • Previous hypersensitivity reaction

Table 2.2 Location and function of the K_{ATP} channels [149]

Subtype	Tissue	Function
K_{ATP} / SUR1	Brain †	• Control of glucose homeostasis • Regulation of neuronal excitability during hypoxia
	Pancreatic cells	• Secretion of insulin from β-islet cells
K_{ATP} / SUR2A	Vascular bed myocytes (vascular smooth muscle)	• Auto-regulation of vessel tone and coronary blood flow • Vasodilatation particularly during episodes of ischemia and hypoxia
K_{ATP} / SUR2B	Sarcolemma of cardiomyocytes	• Control of endogenous cardioprotective mechanism know as "ischemic preconditioning" • Protection of the myocardium during periods of cardiac stress

† At therapeutic plasma concentrations, the sulfonylureas do not cross the blood-brain barrier easily enough to interfere with these channels.

Table 2.3 Intervention studies of sulfonylureas and cardiovascular outcomes

STUDY	POPULATION	INTERVENTION	RESULTS
University Group Diabetes Program UGDP - 1970 Study initiated in 1961, recruitment completed in 1966	N = 1027 Newly diagnosed (≤ 1 year)	Diet and exercise (placebo) *versus* Insulin (variable dose), insulin (fixed dose), tolbutamide or phenformin	No benefit observed on micro- and macrovascular complications after 8.5 years of follow-up. Cardiovascular deaths (total of 61 deaths): · 4.9%(10/205) placebo, 12.7% (26/204) tolbutamide, 6.2% (13/210) fixed dose insulin, 5.9% (12/204) variable dose insulin · tolbutamide treated experienced a significantly higher CV mortality rate compared to placebo group (p = 0.0005) · Increased risk for CV mortality of approximately 1% per year for tolbutamide
Veterans Affairs Cooperative Study - Feasibility Trial 1997 Mean follow-up of 27 months;range 18-25 months	N = 153 men with prevalent type 2 disease and with suboptimal control on insulin or oral agents. Mean age = 60 ± 6.0 years Mean duration of diabetes = 7.8 ± 4.0 years.	"Standard" treatment (i.e., AM insulin) to avoid hyperglycemia or glycosuria *versus* "Intensive" treatment (PM insulin + daytime glypizide, increasing number of insulin injection as needed to maintain glycemic targets) to attain near-normoglycemia	Macrovascular endpoints (only ones studied): · 16/78 (20%) in standard group had at least 1 new CVD event compared to 24/75 (32%) in intensive group (p = 0.10) Feasibility study,therefore insufficient sample size or follow-up to detect a significant difference · Trend toward more event in the intensive multidrug group (with a sulfonylurea) · Overall 6/10 (60%) of deaths were attributable to CVD · 4/9 (44%) of AMI were silent and detected by ECG Hypoglycemia: · Mild to moderate hypoglycemia more common in intensive group (16.5 versus 1.5 per patient-year, p < 0.001) · Severe hypoglycemia uncommon and no difference between groups (2 per 100 patient-year) Miscellaneous: · Strongest predictor of CVD was history of CVD at baseline · Approximately 30% had known CVD at baseline · Nearly 40% had microalbuminuria at baseline

Table 2.3 (cont'd) Intervention studies of sulfonylureas and cardiovascular outcomes

STUDY	POPULATION	INTERVENTION	RESULTS
United Kingdom Prospective Diabetes Study - UKPDS 33 1998 Initiated in 1977 and recruited over 14 years. Median follow-up of 10 yrs for analysis of endpoints; 11.1 yrs for analysis of conventional versus intensive	N= 4209 "Newly treated" type 2 DM (Recruited 5102 but 893 were excluded after a 3-month diet run-in period) Mean age = 53.3 yrs ± 8.6	"Conventional" treatment: · diet and exercise to maintain FBG<15 mmol/L + sulfonylurea or insulin if FBG > 15 mmol/L or symptoms of hyperglycemia occurred *versus* "Intensive" treatment (to maintain FBG<6.0): · sulfonylureas or insulin adjusted to maintain FBG < 6.0mmol/L with combination therapy as needed Monotherapy was be to maintained as long as possible to measure its effect on CVD. Combination therapy consisted of a: · sulfonylurea + metformin or insulin and was introduced only after maximizing therapy with sulfonylurea and only if FBG reached 15mmol/L or symptomatic hyperglycemia developed.	Selected results (macrovascular endpoints for glyburide). Analyses carried out on an 'intent-to-treat' basis: · Fatal MI RR = 0.82 (0.51 - 1.33) · Non-fatal MI RR = 0.74 (0.46 - 1.19) · All AMI RR = 0.78 (0.60 - 1.01) · Sudden death RR = 0.67 (0.21 - 2.16) · Fatal Stroke RR = 1.90 (0.70 - 2.98) · Non-fatal stroke RR = 1.30 (0.71 - 2.98) · Angina RR = 0.84 (0.48 - 1.47) Hypoglycemia · major hypoglycemia - analysis by actual treatment (per year): conventional therapy = 0.1% ; chlorpropamide = 0.4% ; glyburide = 0.6% ; insulin = 2.3% (NB: none of these differences were significantly different)
United Kingdom Prospective Diabetes Study - UKPDS 34 1998	N = 1704 newly diagnosed overweight type 2 diabetes	Conventional treatment (see above) versus Intensive treatment (see above) versus Metformin	Primary analysis of metformin versus conventional treatment: · All AMI - metformin RR = 0.61 (0.41 - 0.89) chlorpropamide or glyburide or insulin RR = 0.79 (0.60 -1.05) · Stroke- metformin RR = 0.59 (0.29 - 1.18) chlorpropamide or glyburide or insulin RR = 1.14 (0.70-1.84) Secondary analysis of metformin versus intensive treatment: · All-cause mortality - metformin RR = 0.64 (0.45 - 0.91) sulfonylurea + metformin RR = 1.60 (1.02 - 2.52) · Diabetes-related mortality - metformin RR = 0.58 (0.67- 0.91) sulfonylurea + metformin RR = 1.96 (1.02-9.75) · All AMI - metformin RR = 0.61 (0.41 - 0.89) sulfonylurea + metformin RR = 1.09 (0.67 - 1.78) · Stroke - metformin RR = 0.59 (0.29 - 1.48) sulfonylurea + metformin RR = 1.21 (0.68 - 2.65)

Table 2.4 Observational studies of cardiovascular outcomes associated with the use of sulfonylureas

Study	Design	Exposure	Primary outcome(s)	Reference group	Results	Comments
Garratt et al. (1999) [130] Study period: 1985 – 1995	Retrospective cohort of individuals undergoing direct coronary angioplasty for treatment of acute MI N = 185 Follow-up: 3.7 (±2.3) years	Source: Medical records + standardized questionnaire Categories: Sulfonylurea (36%) Diet or insulin (64%) Time-window: use at the time of angioplasty (current exposure)	In-hospital deaths (short term survival) Post-discharge or late deaths (long term survival)	Use of diet alone or insulin	Early mortality: Sulfonylurea (24%) vs diet or insulin (11%) (P=0.02); OR 2.53 (95% CI, 1.13-5.67) Late mortality: Not reported except to say that no difference was found between the two groups	Did not account for duration of diabetes, disease progression or severity, or markers of these such as nephropathy, and calendar time. In addition, no distinction made between type 1 & 2 diabetes. The analysis of late mortality was executed on an intent-to-treat basis using exposure at time of angioplasty.
Jollis et al. (1999) [131] Study period: 1994 – 1995	Retrospective cohort of elderly individuals hospitalized with AMI N = 64,171	Source: Medical records Categories: Sulfonylurea (39%) Insulin (29%) Sulf + insulin (4%) Neither agent (28%) Time-window: use at admission (current exposure)	In-hospital complications (CHF, shock, and cardiac arrest) In-hospital deaths	Not treated with either agent	All comparisons are for sulfonylurea: CHF – OR 1.01 (P>0.05) Shock – OR 0.93 (P>0.05) Arrest – OR 0.93 (P>0.05) Death – OR 0.95 (P>0.05)	Did not account for duration of diabetes, disease progression or severity, and did not distinguish between type 1 and type 2 diabetes. No information provided on whether the reference group is diet controlled or receiving other antihyperglycemic agents.
Olsson et al. (2000) [132] Study period: 1984 – 1995	Retrospective cohort of individuals with type 2 diabetes N = 910 Follow-up: 6.1 (±6.0) years	Source: Medical records Categories: Sulfonylurea (81%) SU + MET (19%) Determined at cohort entry	Cause-specific mortality (IHD, stroke) Overall mortality	Use of sulfonylurea monotherapy (never on MET)	Cause-specific mortality: IHD – OR 1.73 (1.17-2.55) Stroke – OR 2.33 (1.17-4.63) Overall mortality: OR 1.63 (1.27-2.09)	Did not account for disease progression or severity or important markers of progression such as the presence of diabetes-related complications.
Klamann et al. (2000) [133] Study period: 1991 – 1997	Retrospective cohort of individuals hospitalized with AMI (with and without diabetes) N = 602 (357 non-diabetic; 80 newly diagnosed type 2 diabetes; and 165 with prevalent type 2 diabetes)	Source: Medical records Categories: Sulfonylurea-based treatment (46%) No sulfonylurea (54%)	In-hospital deaths and size of infarct	Not using a sulfonylurea	In-hospital mortality: Non-diabetics – 20.2% Newly diagnosed – 25.0% Using sulfonylurea – 33.0% No sulfonylurea – 32.9% (differences between treated groups not statistically significant). No clear differences in infarct size observed.	Studying individuals with prevalent type 2 diabetes. Comparisons do not account for baseline differences.

Table 2.4 (cont'd) Observational studies of cardiovascular outcomes associated with the use of sulfonylurea

Study	Design	Exposure	Primary outcome(s)	Reference group	Results	Comments
Fisman et al. (2001) [27]	Prospective follow-up study of individuals with coronary artery disease N = 2275 Follow-up: 7.7 years	Source: Physician interview Exposure: Use of glyburide, metformin or combination therapy. Determined at cohort entry	All-cause mortality. Mortality rates: 58.4 - 79.5/1000 py with prior MI and 18.1 - 63.2/1000 py with no prior MI.	Controlled by diet alone	All-cause mortality (95% CI): Glyburide = 1.22 (1.02-1.45) Metformin = 1.26 (0.81-1.96) Combined = 1.53 (1.20-1.96)	Studying individuals with prevalent type 2 diabetes and did not control for diabetes duration. Comparisons vs those treated with diet alone would be confounded by diabetes progression and severity.
Johnson et al. (2002) [134] Study period: 1991 - 1996	Retrospective cohort of newly treated type 2 diabetes N = 12,272 Follow-up: 5.1 (± 2.2)	Source: Administrative health database Categories: Sulfonylurea monotherapy Metformin monotherapy Combination of both agents Determined at cohort entry but required at least 1 year of use	All-cause mortality	Metformin vs sulfonylurea monotherapy	All-cause mortality: Sulfonylurea monotherapy = 24.7% Metformin monotherapy = 13.8% Oral combination = 13.6%	Most likely biased by improperly accounted for immortal time
Meier et al. (2003) [135]	Prospective follow-up of consecutive MI admissions N = 562	Source: Hospital chart Categories: Sulfonylureas Determined at admission	Post-MI mortality	Receiving any other antidiabetic treatment	All cause mortality: No significant differences observed	Studying individuals with prevalent type 2 diabetes and prevalent exposure.

CHAPTER 3: METHODOLOGICAL CONSIDERATIONS

3.1 Overview of study design

The following is an overview of the main study using a cohort of individuals newly treated with an antihyperglycemic agent (insulin and oral hypoglycemics) to assess the risk of acute myocardial infarction (MI) associated with the use of oral hypoglycemic agents (OHAs).

We defined a population-based cohort of all persons initiating treatment with an antihyperglycemic agent between January 1st, 1978 and December 31st, 1999 to study the possible association between the use of oral hypoglycemic agents and the risk of acute myocardial infarction. The cohort was identified using the computerized health insurance databases of the province of Saskatchewan, Canada. Cohort members were followed until the earliest of the following dates: hospitalization for acute myocardial infarction (study end point), termination of health insurance coverage (due to emigration or death), death, or December 31st, 2001 (end of study). Acute myocardial infarctions (MI) were identified through record linkage of the cohort with the hospital separations database. In view of the large size of the cohort, the time-varying nature of drug exposure, and the potentially confounding effect of calendar time and diabetes duration, we used a nested-case control analysis of these cohort data. For each case of MI, up to 20 controls matched on age, year of cohort entry and duration of diabetes both pre- and post-treatment initiation (ie, prior to cohort entry and days of follow-up respectively), were randomly selected. Information on antihyperglycemic drug exposures and covariates were obtained for all cases and controls using the prescription drugs, the hospital separations, and the physicians' services databases. Rate ratios, adjusted for measured confounders, were estimated using conditional logistic regression to account for the individual level matching.

3.2 Saskatchewan Health Databases

The computerized health insurance databases of Saskatchewan were the source of data for this study. These administrative databases were developed as a result of the universal health care programs offered to residents of this province with no age restriction (ie, from birth to death). Briefly, each Saskatchewan resident (approximately 1 million), with the exception of members of the Royal Canadian Mounted Police,

Canadian Forces and inmates of federal penitentiaries, is assigned a Health Services Number (HSN).[1] The HSN is a lifetime number that uniquely identifies each resident. Since the HSN is included in each of the databases, it enabled record linkage of these databases at the level of the individual. Registered First Nations people and veterans have their prescriptions paid for by federal government agencies and are therefore excluded from the provincial prescription drugs database. Residents who are not captured at all, or are eepresented in only some of the databases represent less than 9% of the province's population.

Five databases were used for the main study: (1) the Population Registry Database which provides information on insurance coverage and socio-demographics, (2) the Prescription Drugs Database for information on out-patient prescription drugs and the identification of certain covariates, (3) the Hospital Separations Database for identification of hospital discharge diagnoses to identify study end points and co-morbidities, (4) the Physician Services Database for information on medical services and procedures to identify certain comorbid conditions, and (5) the Vital Statistics Database for the identification of all deaths. A detailed description of the data available from the various databases is provided in Table 3.1 and details of the research data obtained for the main study is provided in Table 3.2.

3.3 Study cohort

We used the drug codes of the Prescription Drugs Database to identify all registered residents aged 35 years or older who received an antihyperglycemic agent (insulin or oral hypoglycemic agent) between January 1, 1978 and December 31, 1999, and had at least one year of health coverage prior to their first such prescription. The date of this first prescription was taken as cohort entry. To identify newly treated persons, we excluded those who had been dispensed an antihyperglycemic in the year preceding cohort entry and those whose first outpatient prescription occurred during a hospitalization. The latter criterion ensured that the date of cohort entry represented the start rather than the continuation of inpatient initiated treatment given that in-hospital

prescriptions are not captured by the database. Cohort members were followed until December 31, 2001.

For the purposes of determining the person-time contributed by each subject, *time zero* was taken as the date of cohort entry (i.e., date of the first prescription for an antihyperglycemic dispensed during the accrual period). The *exit date* was the earliest of the following dates: first hospitalization for acute MI (study end point), termination of coverage (due to emigration from the province or death), death, or December 31st, 2001 (end of study). Except for the event date, all other end dates were censored. Given the nature of these population-based data, and documented emigration patterns for Saskatchewan, we expected losses to follow-up to be low and due to emigration.

Several decisions were taken in defining the cohort that have methodological implications and thus, require further discussion. First, the period of accrual of 1978 to 1999 was chosen to ensure that the cohort yielded a large number of subjects who also had prolonged follow-up and exposure experience, in order to maximize the number of outcomes observed and span a calendar time period sufficiently long to capture the maximum number of antihyperglycemic agents marketed at the time the main study was planned (2001). Second, we included individuals initiating treatment on insulin because we were uncertain of antidiabetic prescribing trends during the 1970s and early 1980s and of how insulin initiators may differ from those initiating therapy with an oral agent. Third, we used age 35 as a cut point to minimize the number of individuals with type 1 diabetes. Finally, the minimum of one year of prior insurance coverage criterion was used to establish a baseline medical and medication history for all cohort members.

3.4 Bias related issues

Type 2 diabetes is an important but methodologically challenging disease to study using an observational design. The insidious onset of this disease results in most cases being diagnosed secondary to blood glucose screening. This in turns means that the vast majority of cases diagnosed represent prevalent disease with varying degrees of diabetes related complications being present at diagnosis. As a result, a cohort of newly diagnosed

individuals represents a heterogeneous population from the perspective of disease progression and severity, and therefore, risk of macrovascular events. Moreover, the chronic and progressive nature of type 2 diabetes leads to numerous changes in drug therapy over time, with each indicative of disease progression and severity. Finally, both the blood glucose threshold at which a diagnosis is made and the treatment of diabetes has changed over time. All of these factors represent potential sources of bias that need to be carefully considered in observational studies of type 2 diabetes both at the design stage and during the analysis.

In this thesis six important types of bias were addressed: (i) confounding by diabetes progression and severity, (ii) confounding by diabetes duration, (iii) channeling bias due to formulary prescribing restrictions, (iv) residual confounding due to unmeasured risk factors, (v) calendar time bias, and (vi) immortal time bias. The first five were encountered in the main study evaluating the risk of myocardial infarction associated with the use of oral hypoglycemic agents, while the sixth was addressed in a separate study of the effect of cholesterol lowering "statins" on diabetes progression.

Confounding by diabetes progression and severity was addressed both at the design stage and during the analysis. At the design stage, we restricted the cohort to a more homogeneous population of newly treated individuals (ie, all treated cohort) since treatment is usually initiated to control chronically elevated plasma glucose levels. In the analysis we adjusted for the presence of diabetes related complications at cohort entry, used treated individuals as the comparator group, and stratified the analysis by treatment intensity (i.e., monotherapy, oral combination therapy, oral-insulin combinations, and insulin monotherapy). Confounding by diabetes duration was controlled for in the analysis by matching MI cases and their controls on duration of diabetes, pre- and post-treatment initiation separately, and using a matched analysis. Similarly, confounding by calendar time was addressed through matching (year of cohort entry) and the use of a matched analysis. On the other hand, channelling bias was addressed in sensitivity analyses by using comparator groups of increasing diabetes severity and immortal time bias was avoided through the use of proper accounting of person-time of follow-up and

the use of a time-dependent analysis. Finally, residual confounding due to unmeasured risk factors was addressed in a separate study evaluating the confouder-exposure associations and through the use of a simulation-based tool that permitted indirect adjustments of the unmeasured factors.

3.5 Statistical analysis

3.5.1 Choice of analysis

The traditional method of analyzing cohort data is a time-to-event approach using Cox Proportional Hazards regression. All too often however, users of this method determine an individual's exposure status uniquely at baseline (i.e., cohort entry). In such analyses, the exposure of interest is inappropriately analyzed as if it was static and, depending on the nature of the drug under study, can result in significant misclassification bias and, in some instances, immortal time bias.[2] Although cohort analyses using time-dependent covariates are increasingly being used, these can be particularly challenging to execute in pharmacoepidemiologic database studies given the complexity of the time-dependent nature of drug exposure (e.g., on-off usage resulting from non-compliance or non-adherence, switching of agents within and across therapeutic classes, unexplained lag periods or overlaps between prescription fills). This is particularly true in the context of a chronic and progressive disease such as type 2 diabetes. In addition, such analyses tend to be computationally intensive given the large size of study cohorts and long duration of follow-up that are typical of such studies. In order to appropriately assess exposure to oral hypoglycemics in relation to the time of each event (i.e., the etiologically relevant window of exposure) while simultaneously controlling for the effects of diabetes duration and calendar time, we undertook a nested case-control analysis of the cohort.[3, 4] This approach has been shown to provide unbiased estimates of the rate ratios that would be obtained from a time-to-event COX regression analysis of the full cohort, with little or no loss in precision but significant gains in computational efficiency, particularly when analyzing time-varying exposures within large cohorts.[5-7] This is not surprising given that the primary differences between these two analytical techniques is the number of non-cases or controls that is retained in the

analysis and the length of the exposure window that is considered (ie, in proximity to the index date only *vs* all available person-time of follow-up).

3.5.2 Choice of comparator group

The choice of an appropriate comparator group or reference category is critical to the validity of the results. Typically in pharmacoepidemiologic studies, researchers use an unexposed group, either currently unexposed or unexposed in the year preceding the index date, or an actively treated comparator. The advantage of the active comparator is that it controls for the treatment's indication which can be an important source of bias. The disadvantage is that one can only estimate the effect of a treatment relative to that of another agent rather than the true pharmacological effect of the treatment of interest. For example, an increased risk of MI for drug A relative to drug B could be due to drug A being harmful or drug B exerting a beneficial effect. On the other hand, the clinical reality for the management of type 2 diabetes is that treatment choices are made on the bases of choosing *between* treatments, as no treatment is not a viable option once the disease has progressed beyond a certain stage. Furthermore, in the context of a chronic and progressive disease such as type 2 diabetes and an all-treated cohort, such as that used in the main study, it is difficult to know who unexposed individuals represent. The latter could be individuals who have managed to get their disease under control through diet and lifestyle modifications, and hence may be healthier than treated individual, or they could represent individuals who are in denial and therefore avoid further contact with the medical system.[8] Consequently, in our primary analysis we chose to use an active treatment as the comparator; metformin was used as the reference category because it is not known to exert adverse cardiac effects and is as effective as other OHAs at reducing plasma glucose levels.

3.5.3 Covariates

The primary risk factors for the development of cardiovascular events in those with type 2 diabetes are, for the most part, the same as those for non-diabetic individuals and include age, sex, hypertension, smoking, dyslipidemia, family history of coronary heart disease, socioeconomic status (SES) and obesity.[9] However, recent evidence from

the UKPDS,[10] the Diabetes Prospective Trial,[11] and the Diabetes Intervention Study [12] indicates that obesity may not be an independent risk factor for cardiovascular events once the presence of diabetes has been taken into account. Other important independent predictors of cardiovascular disease that are specific to type 2 diabetes include albuminuria at the time of diagnosis (a marker of nephropathy),[9] history of any diabetes-related complications,[13] and duration of diabetes [14].

The computerized health insurance databases previously described allowed for adjustment of concomitant drug therapies associated with the risk of MI and the presence of co-morbidities, including diabetes related complications. Co-morbidities were identified through the use of hospital discharge diagnoses, physicians' services codes, and the dispensing of drugs used in the treatment of such illnesses.

Of the risk factors described above, information on dyslipidemia, SES and intensity of treatment was only partially captured by the health databases, while information on smoking, nutrition, alcohol consumption, and SES was not captured at all. The possibility of residual confounding by these unmeasured risk factors was addressed in two studies accompanying the main study.

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Table 3.1 Description of the Saskatchewan Health Databases

DATABASE	DESCRIPTION	INFORMATION AVAILABLE
Population Registry Database	Contains the identification and demographic details of all eligible residents. Information is also available on duration of coverage and whether a resident has ever received social assistance, a proxy for socioeconomic status	Health Services Number (HSN), sex, marital status, date of birth, date of death (if applicable), location code, indicator for registered Indian status, indicator for current recipients of social assistance (welfare), dates of coverage initiation and termination
Prescription Drugs Database	Contains information on all outpatient and long term care facilities prescriptions dispensed for drug listed in the provincial formulary	HSN, sex, year of birth, designation of special status (e.g., long-term care home resident), pharmacologic-therapeutic classification, drug identification number, active ingredient number, generic and brand names, strength and dosage form, manufacturer, date and quantity dispensed, 'no substitution' designation (if applicable), prescriber ID number, pharmacy ID number and cost information
Hospital Separation Database	Contains data on all hospitalizations for eligible residents and includes reliable information on primary and secondary discharge diagnoses (using ICD-9 codes), inpatient procedures, admission and discharge dates, and vital status at separation.	HSN, sex, month and year of birth, up to 3 discharge diagnoses (ICD-9), up to 3 procedures (CPP), accident code (ICD-9 external cause code), admission and discharge date, level of care codes, length of stay, admission and separation types, case mix group, resource intensity weight, attending physician and surgeon (if applicable), hospital ID number
Physician Services Database	Contains information on physician speciality, referrals, date and type of services (using ICD9-CM codes)	HSN, age, sex, residence code, indicator for registered Indian status, physician specialty, referring physician, clinic, physician: age, sex, place and year of graduation, practice type, date of service, type of service, primary diagnosis, locations of service (e.g., inpatient, outpatient), and billing information
Vital Statistics Database	Contains information on all births, deaths, stillbirth, and marriages	HSN, date of birth, sex, date of event. For deaths the underlying cause and up to 12 contributing causes (using ICD-9 codes)

Table 3.2 Details of the research data

PURPOSE	SOURCE OF DATA	INFORMATION PROVIDED
Cohort formation	Prescription Drugs, Hospital Separations, and Physician Services Databases	· Electronic file of all registered residents (identified by their HSN only) having received at least 1 prescription for an antihyperglycemic agent between 1978 & 1999. · Information provided includes sex, date of birth, date of death (if applicable), geographic location code, indicator for current recipients of social assistance, dates of health insurance initiation and termination. · Complete history of all prescriptions dispensed for any anti-diabetic medication for each subject. · All available data on hospital separations for AMI (ICD-9, 410).
Ascertainment of outcomes	Hospital Separations, Vital Statistics Databases, and death certificates	· Admission and discharge dates and length of stay for each of the following outcome(s): AMI (ICD-9, 410) · Date and cause of death · Above data for each member of the cohort starting as far back as data is available and up to December 31, 2001
Ascertainment & classification of exposure	Prescription Drugs Database	· Electronic file of all prescriptions dispensed for an anti-diabetic medication at the level of the individual agent and for each cohort member · Data to be provided includes therapeutic category, drug identification number, drug name (generic and brand), strength and dosage form, date and quantity dispensed, encrypted prescriber ID number · Above data from January 1, 1976 up to December 31, 2001
Covariates	Hospital Separations, Physician Services, and Prescription Drugs Database	· To identify co-morbidities using ICD-9, ICD-9 CM and a variety of drugs. · Information on drugs that may interfere with the action of hypoglycemics · Information on drugs that may be associated with AMI (e.g., ASA, estrogen replacement therapy, etc.)

CHAPTER 4: ORAL HYPOGLYCEMICS AND ACUTE MYOCARDIAL INFARCTION

4.1 Preface to the manuscript

This chapter contains the first manuscript in a series of three articles on the postmarketing safety evaluation of oral hypoglycemic agents. Specifically, the article presented in this chapter addresses the risk of acute myocardial infarction (MI) associated with the current use of individual oral hypoglycemic agents using data from a large, population-based cohort identified using administrative health databases of the province of Saskatchewan.

As previously discussed, pharmacoepidemiologic database studies have the advantage of being able to study large and unselected populations in a more natural setting than that of randomized controlled trials. Thus, it is possible to study clinically relevant outcomes in a time and cost efficient fashion. This is particularly advantageous for studies of the cardiac effects of oral hypoglycemics, as the vast majority of clinical trials published to date have evaluated the surrogate end point of glycemic control rather than clinically relevant cardiovascular end points such as acute MI. On the other hand, pharmacoepidemiologic studies are particularly vulnerable to confounding bias including confounding by indication. Also, since type 2 diabetes is a chronic and progressive disease, observational studies of this disease and related complications need to pay particular attention to the biasing effect of diabetes duration, and diabetes progression and severity. Ideally, one would like to have information on hemoglobin A1c (HgA1c), a measure of glycemic control which is associated with the risk of diabetes related complications, at least those of small vessels such as retinopathy, neurophathy and nephropathy. As such, HgA1c is a good marker of diabetes progression and severity since individuals whose diabetes progresses will present with consistenty elevated HgA1c. Unfortunately, this laboratory parameter is typically unavailable in administrative health databases.

In the current study, we addressed this methodological challenge by attempting to account for diabetes progression and severity in a variety of ways. First, we made the assumption that physicans treat all individuals with the intent of lowering glucose levels

as close to recommended target levels as is feasible for any given person. Next, given that oral hypoglycemics are equally effective at controlling glucose levels, we assumed that the HgA1c at diagnosis was unlikely to be an important determinant of a physician's choice of agent. We therefore addressed diabetes progression and severity by comparing individuals that were more homogenous in this regard. Consequently, we defined the study cohort as individuals newly treated with an antihyperglycemic agent. In addition, we matched cases and controls on the duration of their diabetes both pre- and post-treatment initiation (ie, duration prior to cohort entry and duration of follow-up). Finally, since the treatment of type 2 diabetes generally follows a stepwise approach that can be used as a proxy for progression and severity, we stratified the analysis according to treatment intensity defined as monotherapy, oral combination therapy, oral-insulin combinations and insulin monotherapy.

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4.2 Oral hypoglycemic agents and the risk of acute myocardial infarction: a population-based cohort study

ORAL HYPOGLYCEMIC AGENTS AND THE RISK OF ACUTE MYOCARDIAL INFARCTION: A POPULATION-BASED COHORT STUDY

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Words: 4,080 **Tables: 5** **Figures: 3**

Running title: OHA and acute myocardial infarction

Keywords: diabetes, myocardial infarction, oral hypoglycemic agents, adverse effects, cohort studies, pharmacoepidemiology.

ABSTRACT

Background: A recent meta-analysis has suggested that rosiglitazone, used in the treatment of type 2 diabetes, may increase the risk of myocardial infarction (MI) and cardiovascular death. The risks of other oral hypoglycemic agents (OHAs) are uncertain.

Methods: We identified a population-based cohort of 42 775 adults, ages 35 and over, initiating treatment with an antihyperglycemic between 1978 and 1999, using the administrative heath databases of the province of Saskatchewan, Canada. The cohort was analyzed using a nested case-control approach with each case of a first MI matched with controls on age, duration of diabetes, duration of follow-up, and year of cohort entry. Rate ratios (RR) for MI associated with the current use of various OHAs were estimated using conditional logistic regression and adjusted for prognostic factors.

Results: During a median follow-up of 6.8 years, 4 806 (11.2%) persons were hospitalized for an acute MI. Current treatment with a thiazolidinedione (TZD), consisting primarily of rosiglitazone, was associated with a significantly increased risk of MI (4 cases; adjusted RR, 3.78; 95% confidence interval [CI], 1.23-11.67; P=0.02) compared with metformin monotherapy (231 cases). The excess risk persisted even when TZD monotherapy was compared with insulin (RR, 2.82; 95% CI, 0.92-8.68; P=0.07). A small increased risk was observed with the use of sulfonylurea monotherapy (870 cases; RR, 1.24; 95% CI, 1.06-1.45; P< 0.01) but not other OHAs (6 cases; RR, 1.11; 95% CI, 0.48-1.45; P=0.80). The use of TZD-insulin and sulfonylurea-insulin combinations were also associated with an elevated risk compared with insulin combinations containing neither agent ([4 cases] RR, 5.06; 95% CI, 1.42-18.00; P=0.01 and [24 cases] RR, 2.42; 95% CI, 1.31-4.47; P< 0.01 respectively).

Conclusions: These results provide further evidence that treatment with rosiglitazone is associated with a clinically important risk of myocardial infarction and new evidence of a risk increase, albeit much smaller, for sulfonylureas.

BACKGROUND

Cardiovascular disease accounts for up to 75% of all deaths in persons with type 2 diabetes and is the major cause of morbidity in this population.[1-4] It is therefore not surprising that given their favourable effects on biomarkers of cardiovascular risk,[5-8] the thiazolidinediones (TZDs) quickly became the most widely prescribed oral hypoglycemic agents (OHAs). Despite early claims of potential cardiovascular benefits, a recent meta-analysis has raised important safety concerns with findings of an increased risk of myocardial infarction (MI) and cardiovascular death associated with the use of rosiglitazone.[9]

On July 30, 2007, a public advisory committee convened by the Food and Drug Administration (FDA) met to review the cardiovascular safety of the TZDs, and rosiglitazone in particular.[10] Panel members voted overwhelmingly in favour of keeping rosiglitazone on the market despite acknowledging the increased cardiovascular risks.[11] The reasons cited for their decision included insufficient evidence linking the drug to MI risk and the belief that other OHAs may pose similar risks. Indeed, concerns regarding the safety of OHAs were first raised in 1970 with the publication of the University Group Diabetes Program (UGDP) study reporting an increased risk of cardiovascular death for tolbutamide and phenformin.[12] The ensuing cardiotoxicity controversy was rekindled in the mid- to late 1990's with the discovery that several endogenous cardioprotective mechanisms, known as ischemic preconditioning, were mediated through the activity of sulfonylurea-adenosine triphosphate-sensitive potassium (SUR-K_{ATP}) channels located in the myocardium.[13-17] The renewed debate coincided with the marketing of the TZDs.

While it is generally accepted that TZDs increase the risk of congestive heart failure (CHF), their effect on MI risk is less clear, particularly as it relates to the risk posed by other OHAs. We conducted a population-based, retrospective cohort study, using data available from a large and unselected population of adults newly treated with an antihyperglycemic, to assess the risk of MI associated with various antihyperglycemic treatments prescribed in routine practice and identify factors that may modify this risk.

METHODS

Study population and data source

We identified a population of adults, ages 35 and older, initiating treatment with an antihyperglycemic (i.e., oral hypoglycemic agent [OHA] or insulin) between 1978 and 1999, using the computerized health insurance and vital statistics databases of the province of Saskatchewan, Canada. These administrative databases, generated by the universal health care programs provided to residents, have been used extensively for research purposes and are described in detail elsewhere.[18] Briefly, we used the population registry, prescription drugs, physician services, hospital services, and vital statistics databases to obtain information on dates of insurance coverage, demographics, outpatient prescriptions, medical services and procedures, hospital discharge diagnoses, and dates and causes of death. Each resident is represented in these databases by an encrypted unique identifier that permits complete record linkage at the level of the individual. Although these data do not clearly distinguish type 1 from type 2 diabetes, the latter represents the majority (> 90%) of cases among adults, particularly in a population being newly treated at age 35 and over.[19-21]

Study design

We conducted a population-based, retrospective cohort study that was analyzed using a time-matched, nested case-control approach.[22, 23] To reduce the potential for confounding by diabetes progression and severity, we selected only persons newly treated for diabetes. As such, the cohort consisted of all residents, 35 years of age and older, who were dispensed an antihyperglycemic between January 1st, 1978 and December 31st, 1999, and had at least one year of health coverage prior to the first such prescription. The date of this first prescription was taken as cohort entry. To identify newly treated persons, we excluded those who had been dispensed an antihyperglycemic in the year preceding cohort entry or whose first prescription occurred during a hospitalization. The latter criterion ensured that the date of cohort entry represented the start rather than the continuation of inpatient initiated treatment since in-hospital prescriptions are not captured by these databases. The remaining individuals were followed until the earliest

of: the date of a first study end point (acute MI), end of coverage (due to death or emigration from the province), death, or end of study (December 31, 2001).

Study end point

The study end point was a first hospitalization with a discharge diagnosis of acute MI (International Classification of Diseases, Ninth Revision code, 410) occurring anytime after cohort entry. This diagnostic code has been previously validated in this database and shown to have 96.9% agreement with the medical chart.[24] The date of admission was taken as the event date (i.e., index date) and the MI was classified as fatal if the individual died within 30 days of admission [25]. For the MI to be considered a valid end point, the duration of the hospitalization had to be at least 3 days, unless the individual had died, been transferred to another institution, or had undergone percutaneous coronary angioplasty.[26, 27]

Antihyperglycemic exposure

We identified all antihyperglycemics covered by the prescription drug plan between 1978 and 2001 and classified them into mutually exclusive categories on the basis of: 1) treatment intensity (i.e., monotherapy, oral combinations, insulin-based combinations), to account for diabetes progression and severity, and 2) their pharmacology, to evaluate the independent effects of TZDs and sulfonylureas (Appendix 4.1). Since only one biguanide, glucosidase inhibitor and meglitinide was available in Canada between 1978 and 2001, these three classes are referred to as metformin, acarbose and repaglinide respectively.

During the study period, the use of TZDs and repaglinide was restricted by the drug plan to individuals who were intolerant, had a contraindication, or were deemed uncontrolled on a sulfonylurea or metformin. As such, only prescriptions dispensed under these conditions were captured by the database and accounted for in our study.

Statistical analysis

The choice and use of drug treatments often change over time, particularly in the context of a chronic and progressive disease such as diabetes. Consequently, drug exposure needs to be analyzed as a time-dependent variable. In order to assess the effects of individual antihyperglycemics in relation to the date of the MI (i.e., the etiologically relevant time period), while simultaneously controlling for the potentially confounding effects of treatment duration, changes in prescribing trends, and duration of diabetes, we used a time-matched, nested case-control analysis of the cohort.[22, 23] This approach has been shown to provide unbiased estimates of the rate ratios that would be obtained from a time-to-event COX regression analysis of the full cohort, with little or no loss in precision but significant gains in computational efficiency, particularly when analyzing large cohorts and long durations of follow-up.[28-30] This approach has been used successfully in previous drug safety studies.[26, 31-33]

Primary analysis

The event date of each case (i.e., index date) was used to define the risk set from which individuals who were still at risk of the event (i.e., non-cases or controls) were chosen. For each case, up to 20 controls matched on age (± 1 year), treatment duration (i.e., days of follow-up), year of cohort entry, and duration of diabetes prior to cohort entry (± 6 months), were randomly selected and assigned an index date that corresponded to the sum of their cohort entry date and the case's duration of follow up. The 87 cases (2.0%) who could not be matched on duration of diabetes within 6 months, were matched with controls whose duration of diabetes was within 6 months to 1 year of that of the case (n = 49 cases) or within 1 to 5 years (n = 37 cases). One case could not be matched on duration of diabetes.

The clinically relevant exposure period analyzed was the year preceding the index date. Assuming a prescription duration of 35 days, individuals were considered currently exposed if their last antihyperglycemic prescription in this one year period lasted until the index date. Past users had filled at least one antihyperglycemic prescription in this time period but were not currently exposed. Current and past users were then categorized into

one of the 14 mutually exclusive groups previously described (Appendix 1). Individuals who had not received any antihyperglycemics in the year preceding their index date were classified as non users during this time period.

To further control for confounding by diabetes progression and severity, we carried out separate analyses according to treatment intensity. For the analysis of oral monotherapy, the risk of acute MI for current users of individual agents was compared with that of current users of metformin monotherapy. The latter was chosen as the comparator because metformin is not known to exert adverse cardiac effects and the OHAs have been shown to be equally effective at reducing plasma glucose.[14, 34, 35] Insulin monotherapy is often used when other treatment regimens have failed to control hyperglycemia. As such, users of this treatment would be expected to have more advanced and severe diabetes than users of other therapies. Since we could not identify an appropriate comparator for insulin monotherapy, its effect on MI risk is not reported. Current users of sulfonylurea-based and TZD-based oral combinations were compared with current users of oral combinations having received neither group of agents. The same approach was used for insulin-based combinations. We estimated unadjusted and adjusted rate ratios (RRs) for these associations using conditional logistic regression to account for individual case-control matching.[36, 37] All rate ratios were adjusted for the potentially confounding effects of well established cardiovascular risk factors, a history of micro- and macrovascular disease, other comorbid conditions, the concomitant use of cardiovascular and other medications, prior hospitalizations, and three measures of health status (the chronic disease score [38], the number of distinct drugs dispensed,[39] and the Charlson index [40]). To control for residual confounding by duration of diabetes, we also adjusted all RRs for this risk factor (0, >0 and ≤1, >1 and ≤2, >2 and ≤5, and >5 years). With the exception of diabetes duration, all covariates were assessed in the year prior to cohort entry (at baseline). Diabetes duration was calculated as the time from diagnosis to cohort entry using a validated administrative data algorithm to identify the date of diagnosis.[41, 42] Medications were identified using the prescription drugs database and comorbid conditions using hospital discharge diagnoses and corresponding drug treatments.

Secondary analysis

Given the prescribing restrictions imposed on the use of TZDs, the clinical profile of these individuals is likely to be more heterogenous than that of users of other oral agents. While individuals with a contraindication or intolerance to other OHAs would tend to be similar to users of metformin monotherapy, those uncontrolled on other agents would likely represent persons with more advanced and severe diabetes. Consequently, in secondary analyses we compared current users of TZD monotherapy with current users of various combinations and insulin monotherapy.

Age, sex, a previous MI, duration of diabetes, and prior antihyperglycemic treatment (i.e., treatment at cohort entry) are all important determinants of an acute MI and as such, may modify the association between OHAs and MI. To test for effect modification, we included an interaction term for each of these factors, one at a time, in subsequent models. All subgroup analyses were carried out using a two-sided test of interaction at a significance level of $\alpha = 0.05$.

Sensitivity analysis

To assess the robustness of our conclusions, we undertook some sensitivity analyses. First, we repeated the analyses using a prescription duration of 90 days. This duration was chosen because, in accordance with the drug plan, some individuals stabilized on chronic therapy may have received a 60 to 90 days supply at a time. In addition, since current users of insulin monotherapy who entered the cohort on this treatment (ongoing users) may have a different cardiovascular risk profile than those who switched to insulin during follow-up (switchers), we repeated the analysis of current TZD monotherapy *vs* insulin using each of these as the comparator.

ETHICS

This study was approved by the Saskatchewan Health Data Access Review Committee and McGill University's Research and Ethics Board.

RESULTS

The study population consisted of 42,775 adults newly treated for diabetes, 46.5% of whom had a diagnosis documented prior to cohort entry (Figure 4.1). Fifty-two percent of these individuals had diabetes for 1 year or less. The mean age (±SD) at cohort entry was 63.8 ± 13.2 years and 54% were male. The vast majority of the study population (97.8%) initiated treatment with monotherapy (Table 4.1). Sulfonylureas were the most commonly prescribed OHAs (68%), followed by insulin (15%) and metformin (14%). In accordance with prescribing restrictions, no one entered the cohort on TZDs or repaglinide. Users of sulfonylureas and metformin were similar with regards to the presence of renal disease, macrovascular disease, other comorbidities and the use of several cardiovascular medications. However, metformin users were somewhat younger, less likely to have retinopathy or neuropathy, and to have been hospitalized in the year preceding cohort entry. They were also more likely to have hypertension and be receiving an antihypertensive. Persons initiating treatment on a combination of either oral agents or insulin, tended to have more advanced and severe diabetes as evidenced by a higher prevalence of micro- and macrovascular disease, prior hospitalizations and higher comorbidity scores.

Cohort members were followed for a median of 6.8 years. During this time, 4,806 persons (11.2%) were hospitalized for an acute MI, 25% of which were fatal. The majority of these deaths (95.6%) occurred prior to discharge. We excluded 485 cases because they occurred during or up to a year after the 18-month period during which the capture of prescription data was incomplete (July 01, 1987 to December 31, 1988). Of the remaining 4,321 cases, one could not be matched on diabetes duration and 4,320 were matched on all criteria with 69,980 controls.

Table 4.2 describes the characteristics of cases of acute MI and their matched controls. As expected, cases were more likely to be male, have micro- and macrovascular disease, and be taking cardiovascular medications. These differences were controlled for in the analyses. On the other hand, cases and controls were well matched with regards to

other important risk factors including age, duration of treatment (i.e., follow-up) and duration of diabetes.

In the year preceding the index date, 71.2% of cases and controls had received at least one antihyperglycemic prescription, of which 41.5% were current users and 29.7% past users (Figure 4.2). The remaining 28.8% were non users during this time period. Most current users were receiving monotherapy (83.6%), primarily with a sulfonylurea (51.1%). There were few users of TZDs, and all but one received rosiglitazone. Similarly, acarbose and repaglinide use was low and therefore, combined for the analysis. Not surprisingly, given the progressive nature of type 2 diabetes, the proportions of users of combination therapies and insulin monotherapy were higher in the year preceding the index date than at cohort entry. Among current users of monotherapy, the vast majority (93.7%) of those treated with a sulfonylurea had initiated treatment with the same agent, while this was the case for only 46.3% and 38.6% of metformin and insulin users respectively (Table 4.3). Eighty-four percent of current users of TZD monotherapy and 59.9% of non users had initiated treatment with a sulfonylurea. Similarly, the majority of users of oral or insulin-based combinations had initiated treatment with a sulfonylurea.

After adjustment for multiple risk factors, current users of TZD monotherapy were at a higher risk of MI than current users of metformin monotherapy (RR 3.78, 95% CI 1.23-11.67) (Table 4.4). We were unable to assess the independent effects of pioglitazone due to its low usage (n=1). The use of sulfonylureas was also associated with an increased risk (RR 1.24, 95%CI 1.06-1.45), though much smaller than that of TZDs. We found no evidence of an elevated risk for those treated with other OHAs (RR 1.11, 95% CI 0.48-1.45). Past users of sulfonylurea monotherapy also appeared to be at higher risk (RR 1.21, 95% CI 1.03-1.42), but not past users of other agents. Persons who did not fill an antihyperglycemic prescription in the year preceding the index date (non users) were 24% less likely to have an MI (RR 0.76, 95% CI 0.65-0.89).

The excess MI risk observed for persons treated with TZD monotherapy persisted regardless of the antihyperglycemic treatment with which it was compared, although

some comparisons were borderline nonsignicant (Figure 4.3). Not surprisingly, the magnitude of the risk was somewhat lower for the insulin monotherapy comparison (RR 2.82, 95% CI 0.92-8.68; p=0.07). We could not assess the effect of oral combinations because there were no cases of MI using the comparator treatment (i.e., neither sulfonylurea nor TZD oral combinations) and none using TZD-based combinations without sulfonylureas. Compared with current users of insulin-based combinations containing neither sulfonylureas nor TZDs, individuals on TZD-insulin combinations were at increased risk for MI (RR 5.06, 95% CI 1.42-18.00), as were users of sulfonylurea-insulin combinations (RR 2.42, 95% CI 1.31-4.47).

No one treated with TZDs was 85 years of age and older or had diabetes for 5 years or more at cohort entry, and only one person had had a previous MI (Table 4.5). Consequently, we could not assess the impact of these factors on the risk of MI. However, the risk was elevated even for persons younger than 85 years, with no history of MI, and with diabetes duration of 5 years or less at cohort entry. The small excess risk observed for sulfonylurea monotherapy was not modified by age, a previous event, diabetes duration, or treatment history. However, women (RR 1.37, 95% CI 1.14-1.65) appeared to be more susceptible to the cardiac effects of these agents then men (RR 1.15, 95% CI 0.97-1.36; p=0.03 for test of interaction).

The results of the sensitivity analysis using a 90 day prescription duration, as well that using ongoing users of insulin monotherapy and switchers to this therapy separately as the comparator group, were essentially the same as those of the primary and secondary analysis.

DISCUSSION

Our study provides further evidence that treatment with TZDs, primarily rosiglitazone, is associated with an increased risk of MI. Of note, this excess risk was observed among persons with no history of a previous MI. Our data also suggest that the risk with TZDs is considerably higher than that associated with the sulfonylureas, whether used as monotherapy or in combination with insulin. Furthermore, the risk of MI

remains elevated even when TZD treatment is compared with insulin-based regimens, suggesting that the excess risk associated with these agents is unlikely to be due to differences in diabetes progression and severity. However, our findings are based on a small number of events for TZD use and the corresponding wide confidence interval results in considerable uncertainty regarding the true magnitude of the risk. Nonetheless, the lower limit of the 95% confidence interval for TZD monotherapy indicates the presence of a clinically important risk, particularly for persons whose baseline rate of cardiovascular events is already 2 to 4 fold higher than that of individuals without diabetes.

An important limitation of previously published studies has been the lack of power to assess clinically relevant outcomes including macrovascular complications. This is due in part to a failure to systematically document cardiovascular events in some large studies,[43] and the recruitment of low-risk populations in others[43-45]. While the recent meta-analysis by Nissen and Wolski[9] addresses, at least in part, the issue of statistical power, their findings require confirmation. Moreover, a FDA drug advisory committee recently highlighted the need for additional evidence on the cardiovascular effects of the OHAs.[11] Our study is the first population-based evaluation of OHAs to confirm the presence of an increased risk of MI associated with the use of TZDs. The use of a large and unselected population of adults, ages 35 and over enabled us to study the effects of TZDs independent of those of sulfonylureas, and obtain results that are generalizable to most adults treated in routine practice. While a major strength of this study has been the use of a time period during which the adverse cardiac effects of the TZDs were unknown and as such, could not have influenced treatment choices, this also contributed to the small sample size for TZD use and the limited power of some analyses.

Our findings for TZDs, are consistent with the results of the recent study by Nissen and Wolski,[9] and an unpublished meta-analysis of rosiglitazone[46]. On the other hand, the apparent small risk increase for sulfonylureas observed in our study has not been previously reported. Although some observational studies have found higher rates of cardiovascular mortality for users of sulfonylureas,[16, 47, 48] others have not,[49-53] and none

have assessed MI risk. In our study, the magnitude of the MI risk was small, present in past users as well, including in the sensitivity analysis using a 90 day prescription duration, and unlike TZDs, disappeared when sulfonylurea monotherapy was compared to insulin-based regimens (data not shown). The greater level of uncertainty about the increased risk for sulfonylureas than for TZDs suggests that these results require confirmation.

The mechanism for the increased risk of MI associated with TZDs has yet to be elucidated, although a number of contributing factors have been proposed. These include, increases in low-density lipoprotein (LDL) cholesterol with rosiglitazone, induced volume overload and myocardial stress, and reduced hemoglobin leading to physiological stress and myocardial ischemia.[9] Alternatively, TZDs have also been shown to inhibit the expression of cyclooxygenase-2 (COX-2) in some tissues.[54-58] As such, these agents could alter the prostacyclin-thromboxane equilibrium in favour of a prothrombic state, similar to that seen with COX-2 inhibitors. On the other hand, the effects of TZDs on COX-2 expression appear to be tissue-specific and have not been studied in the endothelium. Whether the increased risk of MI for TZDs represents a class effect will ultimately depend on the putative mechanism(s).

The small increased risk observed for sulfonylureas is consistent with experimental data suggesting that these agents antagonize the cardioprotective effects of ischemic preconditioning[13] and that they can block the beneficial cardiovascular effects of K_{ATP} channel openers[59]. In contrast, sulfonylureas have also been shown to exert beneficial effects on antiplatelet adhesiveness, endothelial tissue plasminogen activator (TPA) production, and plasma lipoproteins, and inhibit re-entrant arrhythmias.[14, 60-62] More studies are needed to determine the effects of sulfonylureas on clinical end points.

The limitations of our study need to be considered. First, only cases admitted to the hospital were included in our analysis. Missing events due to silent MIs and sudden death could have resulted in incomplete case ascertainment. If this occurred with equal frequency across treatment groups, the resulting misclassification would bias the results

towards the null. Even if TZD use was more likely to induce silent MIs or sudden death, the bias would still be towards the null as TZD exposed cases would be misclassified as exposed controls. Second, we could not identify TZD use for individuals who may have paid for their treatment. However, this would lead to an underestimation of the true risk as users of TZDs would have been classified as non users of this agent. Third, we did not have information on glycosylated hemoglobin. As such, we cannot rule out the possibility of residual confounding even with close matching of cases and controls on a number of important risk factors and the use of analyses stratified by treatment intensity. On the other hand, the increased risk observed for TZD use persisted across all comparisons including insulin-based regimens. Fourth, treatment with TZDs consisted of rosiglitazone in all but one subject and as such, we could not evaluate the independent effects of pioglitazone. Finally, we were unable to reliably assess the potentially risk modifying effects of cardiovascular risk factors, diabetes duration, and prior treatment history owing to the low usage of TZDs.

In summary, our results provide evidence of an increased risk for myocardial infarction with treatment with TZDs, even in individuals with no history of myocardial infarction. Although the observational nature of our study and small number of events for users of TZDs necessitate cautious interpretation, the consistency of the increased risk for various TZD containing regimens, independent of the treatment to which they were compared, together with the evidence from clinical trials leaves little doubt that rosiglitazone is unlikely to exert beneficial cardiovascular effects. Indeed, there is evidence of clinically important harm, particularly when one also considers the increased risk of CHF. Our findings support the need for additional studies to determine if similar risks exist with pioglitazone, assess the timing of this risk, and identify individuals who may be more susceptible to these adverse cardiovascular effects. In the interim, the evidence available to date continues to favour the use of metformin as first line therapy and of pioglitazone when a TZD is indicated.

DISCLAIMER

This study is based on non-identifiable data provided by the Saskatchewan Department of Health. The interpretation and conclusions contained herein do not necessarily represent those of the Government of Saskatchewan or the Saskatchewan Department of Health.

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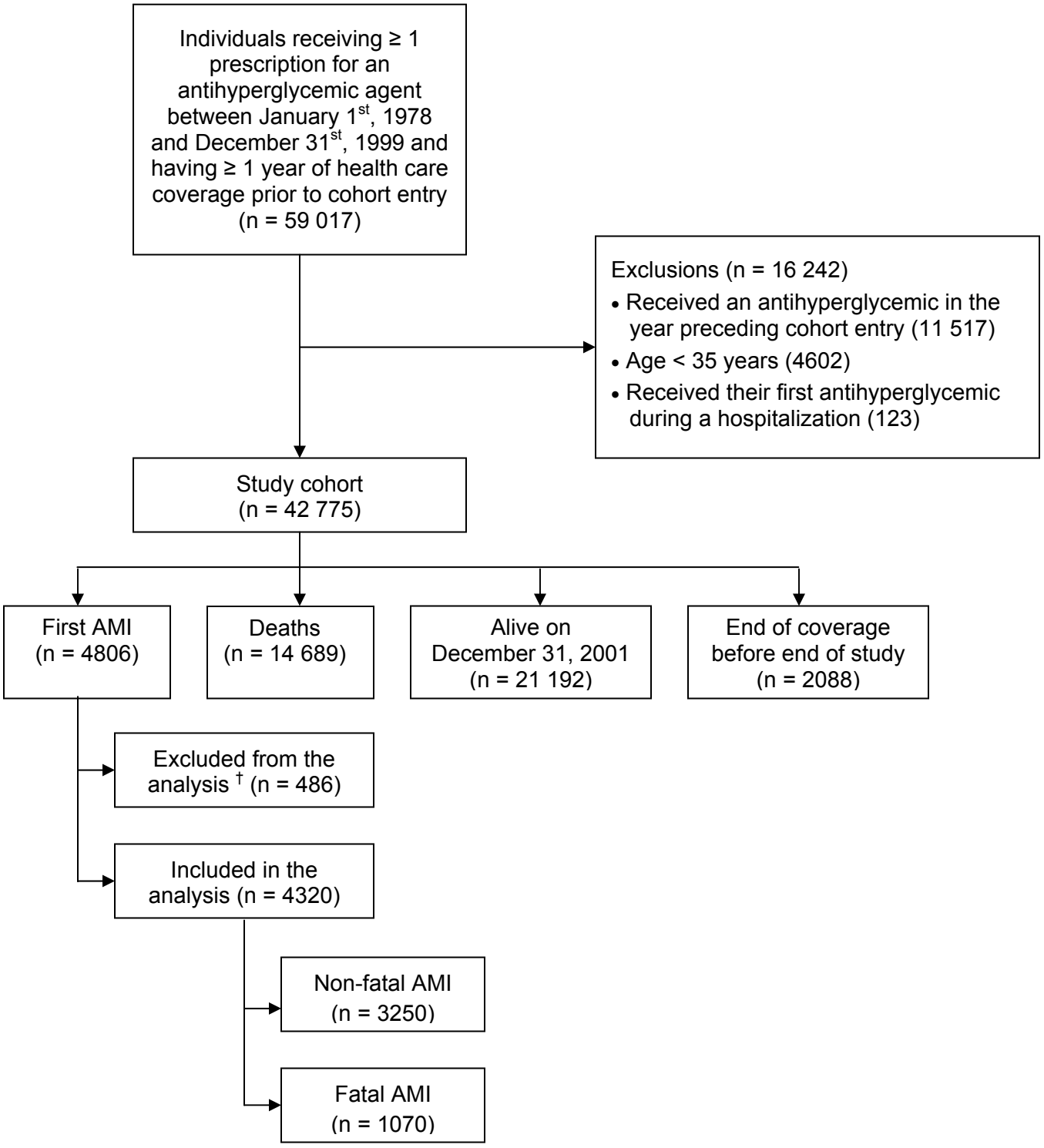

† 485 excluded due to incomplete capture of prescription data between July 01, 1987 and December 31, 1988 and one due to the inability to match on diabetes duration.

Figure 4.1 Study population

Table 4.1 Baseline characteristics of adults newly treated for diabetes [†]

	Monotherapy [*]				Oral combination therapy [*]		Insulin-based combinations [*]	
Characteristics [‡]	**Metformin (n=6107)**	**Sulfonylureas (n=29 016)**	**Acarbose (n=168)**	**Insulin (n=6529)**	**Sulf-based (n=906)**	**Other OHAs (n=7)**	**Sulf-based (n=22)**	**Other OHAs (n=20)**
Age, years	62.2 ± 13.2	65.1 ± 12.7	60.5 ± 12.5	59.9 ± 14.3	63.7 ± 13.2	60.1 ± 15.0	70.5 ± 14.9	66.7 ± 16.8
Male	54.2	54.4	53.6	54.1	58.6	85.7	63.6	45.0
Duration of diabetes [§]								
0 years	54.6	53.4	45.2	56.3	32.8	42.9	27.3	30.0
>0 and ≤1	19.2	22.1	26.8	33.3	49.8	42.9	54.6	35.0
>1 and ≤2	5.1	5.8	7.1	3.0	4.1	14.3	4.6	5.0
>2 and ≤5	11.2	9.9	8.9	4.1	5.6	0.0	9.1	15.0
>5 years	10.0	8.8	11.9	3.3	7.7	0.0	4.5	15.0
Any microvascular disease [‖]	0.4	0.7	0.0	1.4	2.1	0.0	4.6	0.0
Renal disease	0.2	0.3	0.0	0.6	1.2	0.0	0.0	0.0
Macrovascular disease								
Previous MI	5.9	5.7	3.6	5.6	9.7	0.0	4.6	15.0
Previous stroke	1.3	1.6	1.2	2.0	2.9	0.0	0.0	5.0
Previous angioplasty	0.3	0.3	0.0	0.3	0.9	0.0	0.0	0.0
Ischemic heart disease	11.2	11.8	8.3	10.4	15.6	14.3	13.6	30.0
Peripheral vascular disease	1.7	1.6	0.6	2.7	3.0	0.0	4.6	15.00
≥ 2 macrovascular disease	4.3	4.1	2.4	3.9	8.1	0.0	4.6	20.0
Other comorbid conditions								
Hypertension	42.5	39.5	46.4	30.8	39.7	57.1	40.9	40.0
Congestive heart failure	8.8	8.6	6.6	6.9	11.4	28.6	18.2	35.0
Asthma / COPD	10.2	8.4	11.9	8.0	12.5	14.3	31.8	15.0
Depression	13.8	10.9	14.3	9.6	10.7	28.6	31.8	20.0
Cancer	2.8	3.0	3.0	4.2	4.6	0.0	0.0	10.0

Cardiovascular medications								
Beta blockers	13.5	12.6	9.5	10.7	13.1	0.00	9.1	5.0
ACE inhibitors	18.2	8.1	25.6	4.0	15.8	57.1	13.6	40.0
Angiotensin receptor blocker	1.0	0.2	1.8	0.1	0.6	0.0	0.0	0.0
Calcium channel blockers	13.2	7.7	14.8	4.5	13.0	0.0	9.1	15.0
Nitrates	7.7	7.6	6.6	6.0	8.1	14.3	4.6	15.0
Thiazide diuretics	22.3	26.6	23.2	22.7	23.1	28.6	27.3	45.0
Loop diuretics	11.9	11.5	10.7	9.6	13.2	14.3	18.2	30.0
Antiplatelets	0.2	0.2	0.0	0.0	0.7	0.0	0.0	0.0
Aspirin	5.4	6.0	1.8	5.7	4.8	0.0	9.1	5.0
Anticoagulants	4.3	2.6	5.4	2.0	4.3	0.0	4.6	10.0
Statins and fibrates	7.8	3.9	11.9	1.9	5.2	28.6	0.0	5.0
Other medications								
Hormone replacement therapy	6.4	3.8	7.1	3.9	4.3	0.0	0.0	0.0
NSAIDs	14.3	13.0	17.3	11.0	16.4	14.3	13.6	10.0
Oral corticosteroids	8.4	6.6	9.5	6.4	9.5	14.3	22.7	10.0
Measures of general health								
Number of hospitalizations								
None	70.4	64.6	66.7	46.5	32.0	71.4	27.3	20.0
1	20.2	24.7	19.4	39.0	47.4	28.6	59.1	60.0
≥ 2	9.3	10.8	13.7	14.5	20.6	0.0	13.6	20.0
Chronic disease score [¶]	2.7 ± 2.9	2.3 ± 2.7	3.0 ± 3.0	1.9 ± 2.6	2.6 ± 3.0	4.9 ± 4.0	3.5 ± 3.2	3.6 ± 2.8
Charlson index [¶]	0.3 ± 0.8	0.4 ± 0.9	0.3 ± 0.6	0.7 ± 1.1	1.0 ± 1.3	0.3 ± 0.5	1.2 ± 1.0	1.4 ± 1.8
Number of distinct drugs	3.6 ± 3.0	3.3 ± 2.8	3.7 ± 3.1	2.8 ± 2.8	3.4 ± 3.3	4.6 ± 1.2	4.2 ± 3.3	4.6 ± 3.7

Sulf: sulfonylureas; MI: myocardial infarction; COPD: chronic obstructive pulmonary disease; ACE: angiotensin converting enzyme; NSAIDs: nonsteroidal antiinflammatory drugs.
[†] Plus-minus values are means ±SD; all others are percentages (%).
[‡] In the year preceding cohort entry.
***** No one entered on a glitazone or repaglinide.
[§] Percentages may not add up to 100 due to rounding.
[ǁ] Retinopathy, nephropathy, neuropathy.
[¶] Higher scores indicative of poorer health.

Table 4.2 Characteristics of cases of acute MI and their matched controls *

Characteristics †	Cases (n=4320)	Controls ‡ (n=69 980)
Age at index, years	72.2 ± 10.6	72.2 ± 10.3
Male	54.9	45.1
Follow-up, years	6.7 ± 5.2	6.7 ± 5.2
Duration of diabetes		
0 years	46.9	51.2
>0 and ≤1	26.7	22.7
>1 and ≤2	5.8	5.8
>2 and ≤5	10.7	10.7
>5 years	9.9	9.6
Any microvascular disease §	0.9	0.5
Renal disease	0.4	0.2
Macrovascular disease		
Previous MI	11.2	4.5
Previous stroke	1.6	1.8
Previous angioplasty	0.4	0.2
Ischemic heart disease	17.6	10.0
Peripheral vascular disease	2.2	1.4
≥ 2 macrovascular disease	8.0	3.1
Other comorbid conditions		
Hypertension	41.6	39.5
Congestive heart failure	8.2	6.1
Asthma / COPD	8.3	7.2
Depression	8.8	10.1
Cancer	2.2	2.0
Cardiovascular medications		
Beta blockers	16.2	12.8
ACE inhibitors	6.3	6.0
Angiotensin receptor blocker	0.1	0.1
Calcium channel blockers	9.3	6.0
Nitrates	12.1	6.4
Thiazide diuretics	27.3	26.9
Loop diuretics	10.6	9.2
Antiplatelets	0.1	0.1
Aspirin	7.5	5.9
Anticoagulants	2.7	1.9
Statins and fibrates	3.8	3.1
Other medications		
Hormone replacement therapy	2.9	4.2

Other medications cont'd		
NSAIDs	13.5	12.9
Oral corticosteroids	6.0	5.5
Measures of general health		
Number of hospitalizations		
None	58.2	64.4
1	29.9	26.7
≥ 2	11.9	8.9
Chronic disease score ¶	2.4 ± 2.7	2.1 ± 2.5
Charlson index ¶	0.4 ± 0.8	0.3 ± 0.7
Number of distinct drugs	3.4 ± 2.9	3.0 ± 2.6

MI: myocardial infarction; COPD: chronic obstructive pulmonary disease; ACE: Angiotensin converting enzyme; NSAIDs: nonsteroidal antiinflammatory drugs.
* Plus-minus values are means ±SD; all others are percentages (%).
† In the year preceding cohort entry unless otherwise indicated.
‡ To account for case-control matching, all means and percentages for controls were weighted by the inverse of the numbers of controls in each matched case-control set.
§ Retinopathy, nephropathy, neuropathy.
¶ Higher scores indicative of poorer health.

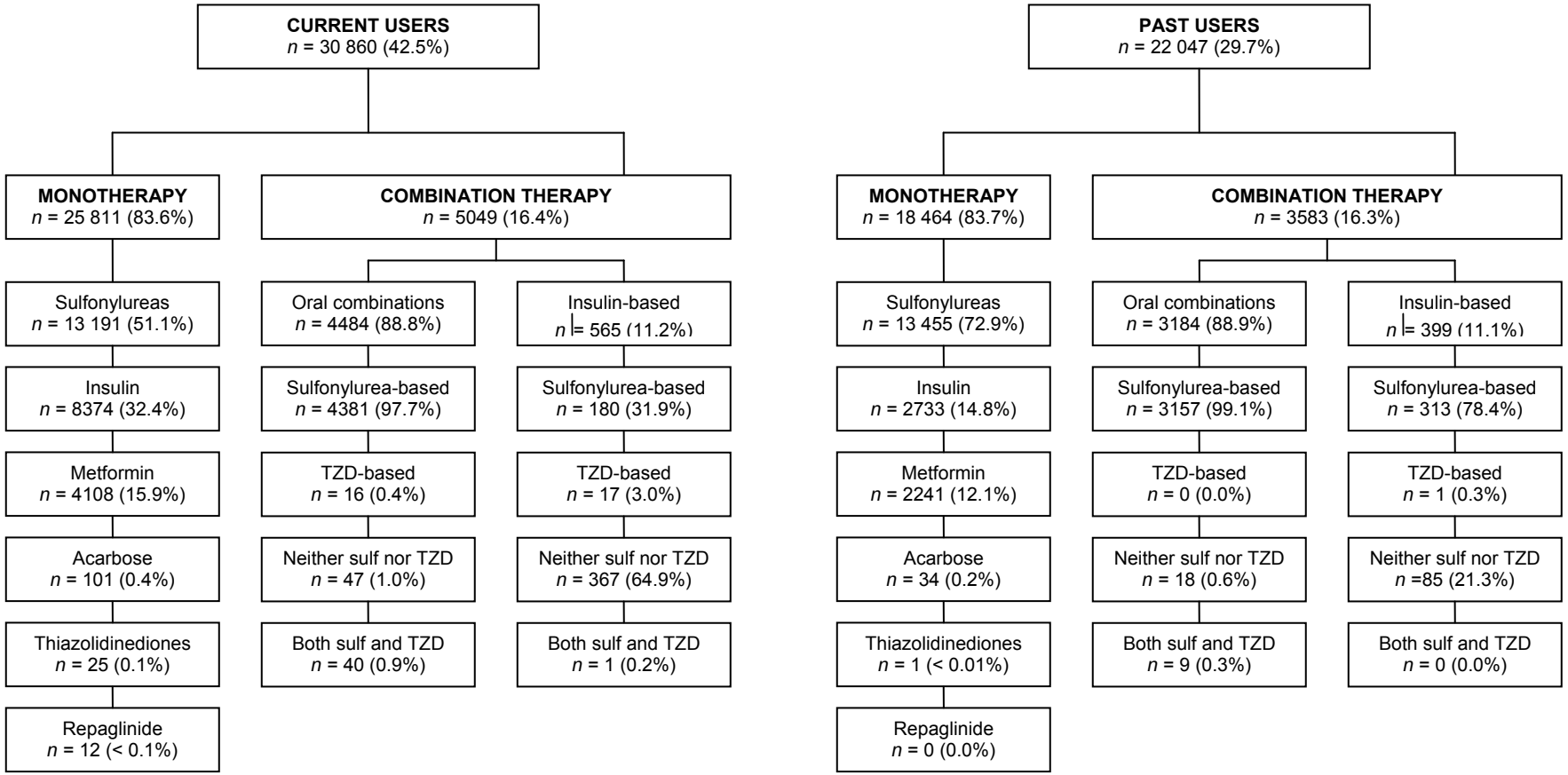

Figure 4.2 Pattern of use of antihyperglycemics in the year preceding the index date

Sulf = sulfonylureas; TZD = thiazolidinediones.

Table 4.3 Pattern of Current Use of Antihyperglycemic and Corresponding Treatment at Cohort Entry

Current use	*n*	Use at cohort entry	*n* (%)
Monotherapy			
Metformin	4108	Metformin monotherapy	1904 (46.3)
		Sulfonylurea monotherapy	1925 (46.9)
		Insulin monotherapy	148 (3.6)
		Oral combination	125 (3.0)
		Other	6 (0.1)
Sulfonylureas	13 191	Sulfonylurea monotherapy	12 357 (93.7)
		Metformin monotherapy	367 (2.8)
		Insulin monotherapy	355 (2.7)
		Oral combination	101 (0.8)
		Other	11 (0.1)
Thiazolidinediones	25	Thiazolidinediones monotherapy	0 (0.0)
		Sulfonylurea monotherapy	21 (84.0)
		Metformin monotherapy	4 (16.0)
Other oral hypoglycemic agents	113	Same agent	33 (29.2)
		Sulfonylurea monotherapy	55 (48.7)
		Metformin monotherapy	18 (15.9)
		Oral combination	3 (2.7)
		Other	4 (3.5)
Oral combination therapy			
Sulfonylurea-based	4381	Sulfonylurea monotherapy	3447 (78.7)
		Metformin monotherapy	469 (10.7)
		Insulin monotherapy	183 (4.2)
		Oral combination	274 (6.3)
		Other	8 (0.2)
Thiazolidinedione-based	16	Sulfonylurea monotherapy	11 (68.8)
		Metformin monotherapy	4 (25.0)
		Insulin monotherapy	1 (6.2)
Neither class	47	Sulfonylurea monotherapy	30 (63.8)
		Metformin monotherapy	9 (19.1)
		Insulin monotherapy	3 (6.4)
		Other	5 (10.6)
Both classes	40	Sulfonylurea monotherapy	25 (62.5)
		Metformin monotherapy	9 (22.5)
		Insulin monotherapy	2 (5.0)
		Other	4 (10.0)
Insulin-based combination therapy			
With sulfonylureas	180	Sulfonylurea monotherapy	150 (83.3)
		Metformin monotherapy	6 (3.3)
		Insulin monotherapy	22 (12.2)
		Oral combination	2 (1.1)
With thiazolidinediones	17	Sulfonylurea monotherapy	9 (52.9)
		Metformin monotherapy	5 (29.4)
		Insulin monotherapy	2 (11.8)
		Oral combination	1 (5.9)
Neither class	367	Sulfonylurea monotherapy	235 (64.0)
		Metformin monotherapy	35 (9.5)
		Insulin monotherapy	87 (23.7)
		Oral combination	8 (2.2)
		Other	2 (0.5)

Both classes	1	Sulfonylurea monotherapy	1 (100.0)
Insulin monotherapy			
Any insulin monotherapy	8374	Insulin monotherapy	3231 (38.6)
		Sulfonylurea monotherapy	4870 (58.2)
		Metformin monotherapy	203 (2.4)
		Oral combination	63 (0.7)
		Insulin-based combination	7 (0.1)

Table 4.4 Unadjusted and Adjusted Rate Ratios of Acute Myocardial Infarction for Monotherapy Using Various Oral Hypoglycemic Agents

	Cases (n =4,320)	Controls (n =69,980)	Unadjusted Rate Ratio	Adjusted * Rate Ratio (95% CI)
Current users †				
Metformin	231	3877	1.00	1.00 (reference)
Sulfonylureas ‡	870	12 321	1.21	1.24 (1.06-1.45)
Glitazones §	4	21	3.59	3.78 (1.23-11.67)
Other OHAs ‖	6	107	1.04	1.11 (0.48-2.61)
Past users †				
Metformin	107	2134	0.85	0.87 (0.68-1.11)
Sulfonylureas ‡	871	12 584	1.18	1.21 (1.03-1.42)
Glitazones §	0	1	--	--
Other OHAs ‖	1	33	0.62	0.70 (0.09-5.17)
Non users ¶	781	20 612	0.71	0.76 (0.65-0.89)

95% CI = 95% confidence interval; OHAs = oral hypoglycemic agents.
* Adjusted for age at index, sex, duration of diabetes (0, >0 and ≤1, >1 and ≤2, >2 and ≤5, and >5 years); presence of microvascular disease, history of nephropathy; previous myocardial infarction, stroke, angioplasty, history of ischemic heart disease, peripheral vascular disease, ≥2 macrovascular disease; history of hypertension, congestive heart failure, asthma and/chronic obstructive pulmonary disease, depression and cancer; concomitant use of beta-blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, nitrates, thiazide and loop diuretics, antiplatelets, aspiring, anticoagulants, statins and/or fibrates, hormone replacement therapy, nonsteroidal antiinflammatory drugs and oral corticosteroids; number of hospitalizations (none, 1, ≥2), chronic disease score, charlson index, and the number of distinct medications used. All covariates were assessed in the year preceding cohort entry.
† An additional 1,024 cases and 12,399 controls who were current users of combination therapy or insulin monotherapy and 425 cases and 5,891 controls past users of these treatments were accounted for in the analysis.
‡ 90% were using glyburide.
§ Only 1 person was using pioglitazone. All other glitazone monotherapy users received rosiglitazone (n = 25).
‖ 12 (8%) of these individuals received repaglinide (all current users) and the remaining 135 (92%) were using acarbose.
¶ Non users were those who had not received any antihyperglycemic prescriptions in the year preceding the index date.

	Cases	Controls	Adjusted RR (95% CI)	P-value
Metformin monotherapy	231	3877	1.00 (reference)	
TZD monotherapy	4	21	3.78 (1.23-11.67)	0.02
Non-TZD oral combination	324	4104	1.00 (reference)	
TZD monotherapy	4	21	2.82 (0.92-8.67)	0.07
Other OHA insulin combination	24	343	1.00 (reference)	
TZD monotherapy	4	21	3.54 (1.07-11.72)	0.04
Non-TZD insulin combination	48	499	1.00 (reference)	
TZD monotherapy	4	21	2.47 (0.78-7.86)	0.13
Insulin monotherapy	644	7730	1.00 (reference)	
TZD monotherapy	4	21	2.82 (0.92-8.68)	0.07

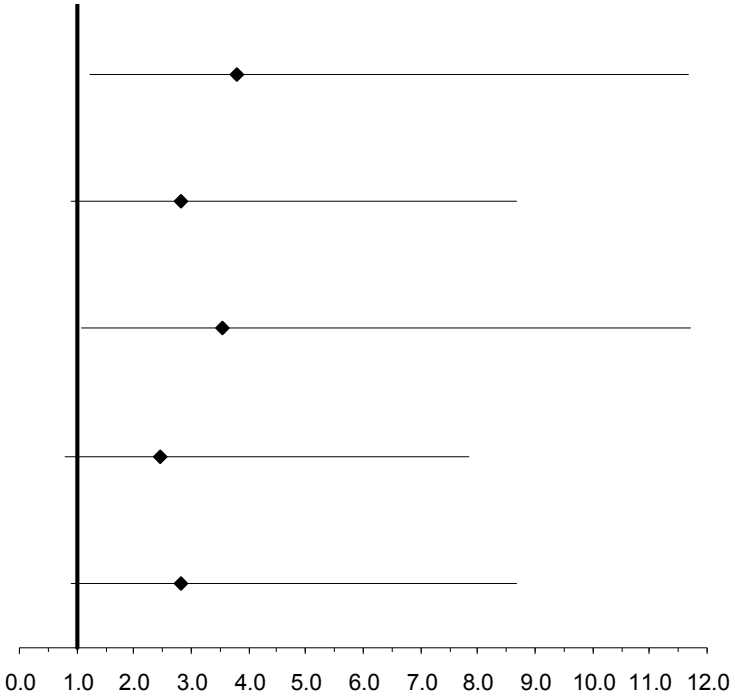

Figure 4.3 Adjusted Rate Ratios of Myocardial Infarction for Current Use of Thiazolidinedione Monotherapy Compared to Current Use of Various Antihyperglycemic Regimens Not Containing Thiazolidinediones

Table 4.5 Adjusted Rate Ratios of Acute Myocardial Infarction for Current Use of Thiazolidinedione and Sulfonylurea Monotherapy According to the Presence of Cardiovascular Risk Factors and Prior Antihyperglycemic Treatment

	Current use of thiazolidinedione monotherapy				Current use of sulfonylurea monotherapy			
	Cases	Controls	Adjusted RR * (95% CI)	P-value †	Cases	Controls	Adjusted RR * (95% CI)	P-value †
Age								
< 85 years	4	21	3.84 (1.25-11.82)	NA	111	1249	1.22 (1.04-1.43)	0.47
≥ 85 years	0	0	--		759	11 072	1.34 (1.02-1.77)	
Sex								
Male	3	9	5.12 (1.27-20.68)	0.53	504	6288	1.15 (0.97-1.36)	0.03
Female	1	12	2.34 (0.30-18.19)		366	6033	1.37 (1.14-1.65)	
Previous MI								
Yes	1	0	--	NA	119	619	1.44 (1.10-1.88)	0.17
No	3	21	3.35 (0.98-11.40)		751	11 702	1.21 (1.03-1.42)	
Diabetes duration								
< 5 years	4	21	3.83 (1.24-11.83)	NA	97	415	1.24 (1.06-1.46)	0.75
≥ 5 years	0	0	--		773	11 906	1.19 (0.88-1.60)	
Initiated with same ‡								
Yes	3	18	2.90 (0.79-10.60)	0.38	817	11 540	1.13 (0.96-1.34)	0.53
No	1	3	9.32 (0.95-91-67)		53	781	1.25 (0.91-1.73)	

RR= rate ratio; CI = confidence interval; MI = myocardial infarction.

* Adjusted for age at index, sex, duration of diabetes (0, >0 and ≤1, >1 and ≤2, >2 and ≤5, and >5 years); presence of microvascular disease, history of nephropathy; previous myocardial infarction, stroke, angioplasty, history of ischemic heart disease, peripheral vascular disease, ≥2 macrovascular disease; history of hypertension, congestive heart failure, asthma and/chronic obstructive pulmonary disease, depression and cancer; concomitant use of beta-blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, nitrates, thiazide and loop diuretics, antiplatelets, aspiring, anticoagulants, statins and/or fibrates, hormone replacement therapy, nonsteroidal antiinflammatory drugs and oral corticosteroids; number of hospitalizations (none, 1, ≥2), chronic disease score, charlson index, and the number of distinct medications used. All covariates were assessed in the year preceding cohort entry.

† P-value for two-sided test of interaction comparing those with and without the prognostic factor at a significance level of $\alpha = 0.05$.

‡ In keeping with prescribing restrictions, all current users of TZD monotherapy initiated treatment on another OHA. Here comparison for both current treatments is having initiated treatment with a sulfonylurea or not.

Appendix 4.1 Antihyperglycemic exposure categories

Pattern of use	Exposure category	Antihyperglycemic agent
Monotherapy	Biguanide	Metformin
	Glucosidase inhibitors	Acarbose
	Meglitinides	Repaglinide
	Sulfonylureas	Acetohexamide, chlorpropamide, glicazide, glyburide, tolbutamide
	Thiazolidinediones (glitazones)	Pioglitazone, rosiglitazone
	Insulins	All insulins
Oral combination therapy	Sulfonylurea-based	Sulfonylurea + ≥ 1 other OHA (not glitazones)
	Glitazone-based	Glitazone + ≥ 1 other OHA (not sulfonylureas)
	Other oral combination	≥ 2 OHAs (not glitazones or sulfonylureas)
	Both sulfonylurea and glitazone-based	≥ 2 OHAs (including glitazones and sulfonylureas)
Insulin-based combination therapy	Sulfonylurea-based	Insulin + ≥ 1 OHA including sulfonylureas (not glitazones)
	Glitazone-based	Insulin + ≥ 1 OHA including glitazones (not sulfonylureas)
	Other insulin combination	Insulin + ≥ 1 OHA (not glitazones or sulfonylureas)
	Both sulfonylurea or glitazone-based	Insulin + ≥ 2 OHAs including glitazones and sulfonylureas

4.3 Additional discussion

In this study particular care was taken to control for the potentially biasing effects of confounding by calendar time and confounding by diabetes progression and severity, as these two sources of bias were believed to be important threats to the validity of such a study and major limitations of previous observational studies.

Confounding by calendar time was controlled for by matching cases and controls on their year of cohort entry (ie, year of treatment initiation) and using a matched analysis. Our *a priori* hypothesis was that calendar time was an important source of bias given that individuals diagnosed later in the study period ought to be both at lower risk of myocardial infarction (ie, diagnosed at an earlier stage of diabetes) and more likely to receive intensive therapy using metformin. However, the analysis unmatched for calendar time (but otherwise identical) yielded the same results as that matched on this factor (data not shown). There are several potential explanations for the apparent lack of confounding by calendar time. First, the various published guidelines driving practice changes over time may not have had the expected impact on physicians' practices. Second, studying a more homogenous population with regards to diabetes progression and severity (ie, all requiring a pharmacological intervention to control their diabetes) may have diminished the impact of these time trends. Finally, matching may have been insufficiently tight to control calendar time bias resulting in a similarly biased matched and unmatched estimate. The latter is unlikely to be the case as we would have expected some difference between the two estimates even with residual confounding. In addition, only two Canadian practice guidelines were published between 1978 and 2001 resulting in only three important shifts in practice during the study period: pre-1992, 1992 to 1998, post-1998.

Confounding by diabetes progression and severity was also addressed at both the design and analysis stage. Since we had no information of HbA1c, we controlled for several other indicators of diabetes progression and severity. First, we studied a more homogeneous population of all newly treated individuals. Second, we matched on

duration of diabetes both prior to and post-treatment initiation, and used a matched analysis. Separate matching for pre- and post-treatment initiation was used because the rate of diabetes progression may not be the same for these two stages of the disease. Third, we used treated individuals as the comparator group in all analyses and adjusted for the presence of diabetes related complications at baseline. Finally, the analyses were carried out separately according to treatment intensity (ie, monotherapy, oral combinations, insulin-based combinations, and insulin monotherapy). Using these approaches, we observed an increased risk of MI for current users of sulfonylurea and of TZD, either as monotherapy or in combination with insulin, with the risk increase being higher for TZDs. However, we also found an increased risk for past users of sulfonylureas, regardless of how far back in the past these agents had been used (data not shown). On the other hand, past users of other oral agents (ie, repaglinide and acarbose) were not at increased risk compared with metformin. Unfortunately, there were no past users of TZDs with which to compare the observed pattern of risk. The latter suggests that the increased risk observed for past users of sulfonylureas is unlikely to be explained by a lower risk of MI among users of metformin. Consequently, the possibility of residual confounding needs to be considered particularly given that we did not have information on some important determinants of MI such as obesity, smoking, alcohol consumption, education, income, and physical activity.

The next chapter provides a quantitative assessment of the potential for residual confounding due to unmeasured risk factors.

CHAPTER 5: ASSESSING THE POTENTIAL FOR INDICATION BIAS

5.1 Preface to the manuscript

This chapter contains the second manuscript in a series of three articles on the postmarketing safety evaluation of the oral hypoglycemic agents (OHAs). Specifically, the article presented here evaluates the potential for residual confounding by indication due to unmeasured risk factors in the OHA-myocardial infarction (MI) associations observed in the main study. Additional discussion is provided in section 5.3.

Typically in database studies, researchers provide a qualitative assessment of the potential for residual confounding by indication due to unmeasured risk factors based on knowledge of prescribing trends in general or those specific to the agent(s) under study. For example, we know that, generally speaking, an individual's smoking status is unlikely to be an important independent determinant of treatment choice as smoking does not affect the benefits or risks associated with the vast majority of prescribed medications. Similar reasoning could be used to discuss the influence of obesity, physical activity, and alcohol consumption on treatment choice. In addition, under a program of universal drug coverage, income would not likely be a strong determinant of prescribing choice, particularly when choosing amongst agents of similar cost. However, some of these qualitative arguments may not be valid for observational studies of pharmacological interventions in the treatment of type 2 diabetes.

Metformin is considered to be the OHA of first choice for the treatment of obese persons with type 2 diabetes. This means that metformin users could be at higher risk of MI compared with users of other OHAs. This could introduce residual confounding by indication in studies in which an individual's body mass index (BMI) is unavailable. Yet, it is difficult to predict the magnitudes of this bias because 75-80% of diabetics are initially treated with a sulfonylurea eventhough 60-70% of them are obese. In addition, obesity is likely to be correlated with several other unmeasured risk factors including smoking, alcohol consumption, education, income and physical activity.

In the current study, we undertook an evaluation of the potential for indication bias due to selective prescribing by factors that are typically unavailable in database studies.

This article will be submitted for publication and should be referenced as follows:

Lévesque LE, Dell'Aniello S, Suissa S. An assessment of the potential for indication bias in observational studies of the treatment of type 2 diabetes. Unpublished manuscript. Montreal: Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, 2007.

5.2 An assessment of the potential for indication bias in observational studies of the treatment of type 2 diabetes

AN ASSESSMENT OF THE POTENTIAL FOR INDICATION BIAS IN OBSERVATIONAL STUDIES OF THE TREATMENT OF TYPE 2 DIABETES

Linda E. Lévesque BScPhm, MSc; Sophie Dell'Aniello MSc;
Samy Suissa PhD

Words: 2,349 **Tables: 4** **Figures: 0**

Running title: Indication bias and type 2 diabetes

Keywords: bias (epidemiology), indication bias, confounding, pharmacoepidemiology

ABSTRACT

Background: Indication bias can threaten the validity of observational studies when information on important risk factors is unmeasured or unavailable. However, the potential for indication bias can be assessed using information on the determinants of prescribing choices obtained from a representative population.

Objective: To assess the potential for indication bias in observational studies of the treatment of type 2 diabetes and the risk of myocardial infarction (MI).

Methods: We used cross-sectional data from the National Population Health Survey (NPHS) of Canada, to identify users of oral hypoglycemic agents (OHAs) and extract information on their socio-demographics, comorbidities, medication use, health care utilization, and health and lifestyle status. The associations between the choice of individual OHAs and several important determinants of MI were estimated using cross-tabulations and logistic regression.

Results: Among the 17,626 respondents of the in-depth health questionnaire, 1315 (7.5%) reported taking an OHA in the month preceding the interview, with sulfonylureas being the most commonly prescribed agent. Compared with users of metformin, users of sulfonylureas were less likely to have a lower level of education (adjusted OR 0.63, 09% CI 0.27-1.49) and low income (OR 0.34, 95% CI 0.11-1.04). They were also less likely to be obese (OR 0.67, 95% CI 0.20-2.22) and be physically active (OR 0.77, 95% CI 0.31-1.92). On the other hand, users of sulfonylureas were more likely to be smokers (OR 2.79, 95% CI 0.79-9.83) and regular drinkers (OR 2.92, 95% CI 0.69-12.27).

Conclusions: We identified a number of potentially important sources of indication bias that will need to be accounted for in future observational studies of oral hypoglycemics and the risk of MI. The overall impact of these sources of bias will need to be assessed quantitatively given that they differed in magnitude and direction.

BACKGROUND

Observational studies of drugs effects have made significant contributions to the improvement of public and population health over the past two to three decades. For example, some pharmacoepidemiologic studies have identified previously unknown but potentially life-threatening adverse drug effects,[1-5] while others have refuted the presence of suspected adverse effects[6, 7] and identified unexpected beneficial effects[8, 9]. On the other hand, pharmacoepidemiologic studies, using large administrative health claims databases, have also been the source of considerable controversy because of their limited ability to control some potential sources of bias. Indication bias or confounding by indication due to selective prescribing is an example of this. This bias arises when the presence of a prognostic factor, or comorbidity, or the perceived risk of a particular outcome influences the decision to prescribe a given drug or drug class.[10] When this occurs, the factor that modified the prescribing decision becomes independently associated with both the risk of the outcome and the probability of exposure. The resulting lack of comparability of the treatment groups being studied threatens the validity of the results whenever information on important determinants of prescribing choices is unmeasured or unavailable.

A potential limitation of large administrative health databases is that they typically lack information on important determinants of health outcomes including socio-demographics, health behaviours and lifestyle factors. However, this will only introduce confounding bias when these unmeasured factors are also associated with the exposure(s) under study. For example, in a database study of the risk of acute myocardial infarction (MI) associated with the use of sulfonylureas compared with metformin, the lack of information on obesity could lead to residual confounding since metformin is the preferred agent for obese persons with type 2 diabetes, and obesity is an important determinant of MI.[11-13] The validity of such a study depends, in part, on the strength and direction of the metformin-obesity association. Consequently, studies quantifying the associations between unmeasured risk factors and exposure to sulfonylureas and metformin need o be carried out to determine the validity of such a study. In addition, it has been suggested that the effect of an unmeasured confounder can be “externally

adjusted" using information about the prevalence of the potential confounder across exposure groups, or the strength of the exposure-confounder association, obtained from surveys of the underlying source population.[14, 15]

We analyzed data from the Canadian National Population Health Survey (NPHS) to assess and quantify the potential for indication bias in database studies of pharmacologic interventions for the treatment of type 2 diabetes by comparing the exposure-confounder associations of users of sulfonylureas with those of users of metformin.

METHODS

Data source and study population

The National Population Health Survey (NPHS) collects detailed socio-demographic information from a representative sample of 58,439 Canadian households and in-depth health information from 17,626 persons, aged 12 years and over, randomly selected within each household.[16] Individuals living on Indian Reserves, Canadian Military Forces Bases, and some remote areas of the province of Québec and Ontario are excluded. Data collection began in 1994 (cycle 1) and is repeated at two-year intervals. The NPHS uses a stratified two-stage sample design to sample households within geographic and socio-economic clusters and supplemental samples are used to compensate for sample attrition between surveys. Data are collected from the respondents by means of a "computer assisted interview" system using highly trained telephone interviewers and a field tested structured questionnaire. All information is obtained from self-report, however, drug names are recorded from medication bottles for both prescription and over-the-counter medications. The survey has a very high response rate (between 90% and 99%) and a high degree of data completeness. The major reason for missing information is ineligibility to answer a particular question (e.g., use of hormone replacement therapy in male respondents). Details of the NPHS sampling scheme, methodology, questionnaire and data accuracy have been previously published.[16]

We used cross-sectional data from the first three survey cycles (1994/95, 1996/97, 1998/99) to identify the subset of respondents who reported using an oral hypoglycemic agent (OHA) in the month preceding the interview. Detailed information on demographics, socio-economic status, comorbid conditions, medication use, health services utilization, and health and lifestyle factors were extracted for these individuals. Binary and categorical variables were used when available and continuous variables were dichotomized using cut-offs corresponding to those used in studies of the determinants of MI. The 1994-1999 time span captures last six years of the time period for a planned observational database study of OHAs and MI risk.

Statistical analysis

The prevalence of important determinants of acute MI that are typically unavailable in administrative heath databases were obtained by calculating the proportion of OHA users who had a specific risk factor. To estimate the associations between the choice of an OHA and several potential determinants of prescribing, we carried out cross-tabulations of various prognostic factors for acute MI by individual OHA (i.e., sulfonylureas, metformin and others). The strength and direction of these exposure-confounder associations were estimated by modelling the probability of being a user of sulfonylureas using logistic regression. Crude and, age and sex adjusted, odds ratios (OR) were estimated. These steps were repeated for each survey cycle analyzed. Although there was some variation in the prevalence of comorbidities and medication use across the three cycles, socio-economic and health and lifestyle factors were essentially the same. As such, only data from the 1996/97 survey are presented here.

In order to account for the complex nature of the survey's multi-stage sampling strategy, and derive meaningful estimates that are representative of the Canadian population, the data were weighted according to Statistics Canada's guidelines for sample weighting.[16] Because the sampling strategy also affects the variance of an estimate, the variance could not be calculated using standard methods and a re-sampling technique had to be used. The "bootstrap" re-sampling method was used to calculate exact individual variances using the sampling weights provided by Statistics Canada

All analyses were performed using Statistical Analysis Software (SAS) version 9.1.3 for windows.

ETHICS

This study was approved by the Research and Ethics Board of McGill University.

RESULTS

Among the 17,626 respondents of the in-depth health questionnaire in 1996/97, 1315 (7.5%) reported taking at least one OHA in the month preceding the interview. Seventy-eight percent (78%) of these individuals were being treated with monotherapy, and 22% with combination therapy. Among those receiving monotherapy, sulfonylureas were the most commonly prescribed agents (71.2%), followed by metformin (18.2%) and other oral agents (10.5%). The vast majority of combination therapies were users of sulfonylureas and metformin. Since the objective of the current study was to evaluate the exposure-confounder associations for sulfonylurea use compared with metformin, no further analyses of users of combination therapy were undertaken.

Table 5.1 displays the prevalence of potential confounders for important determinants of health outcomes that are typically unmeasured in health databases. More than half of the users of sulfonylureas and metformin had high school education or less, 36% were obese, 20% lived at or below the poverty threshold, 14% were smokers, and 11% perceived their health to be poor.

The distribution of demographic and socio-economic factors for users of sulfonylureas compared with metformin, as well as the exposure-confounder odds ratio (ECOR) for these associations are shown in Table 5.2. Generally speaking, most of the exposure-confounder associations evaluated were either unaffected or somewhat attenuated after controlling for age and sex. As such, only adjusted estimates are presented. Sulfonylurea users were considerably older (adjusted OR 2.68, 95% Confidence Interval [CI] 1.27-5.57) than users of metformin and were less likely to be

working (OR 0.61, 95% CI 0.22-1.72). On the other hand, they were less likely to have a lower level of education (OR 0.63, 95% CI 0.27-1.49), and a low income (OR 0.34, 95% CI 0.11-1.04).

Compared with persons prescribed metformin, users of sulfonylureas were somewhat more likely to report having a respiratory illness (adjusted OR 1.23, 95% CI 0.40-3.77), arthritis and rheumatism (OR 1.13, 95% CI 0.50-2.53), and a thyroid disorder (OR 1.19, 95% CI 0.20-7.04), and considerably more likely to report having gastrointestinal ulcer disease (OR 7.02, 95% CI 1.18-41.87) and cataracts or glaucoma (OR 2.36, 95% CI 0.70-7.96) (Table 5.3). Sulfonylurea users were also more likely to be treated with corresponding medications. In contrast, users of sulfonylureas were less likely to have heart disease (OR 0.47, 95% CI 0.20-1.12) and be receiving heart medications (OR 0.36, 95% CI 0.14-0.92) and diuretics (OR 0.70, 95% CI 0.18-2.73).

Table 5.4 compares users of sulfonylureas and metformin according to health and lifestyle factors typically unavailable in pharmacoepidemiologic database studies. There was no difference between users of either agent with regards to self-perceived health status, with two-thirds of individual in either treatment group reporting fair to good health. On the other hand, users of sulfonylureas were more likely to report being current smokers (OR 2.79, 95% CI 0.79-9.83), regular drinkers (OR 2.91, 95% CI 0.69-12.27) and being less physically active than metformin users (OR 0.77, 95% CI 0.31-1.92), but they were also considerably less likely to be obese (OR 0.67, 95% CI 0.22-2.22).

DISCUSSION

We observed a number of potentially important exposure-confounder associations for determinants of MI that are typically unavailable in health databases. The potential confounders included education, income, smoking status, alcohol consumption, obesity, and physical activity. While the strength of any one of the observed associations is sufficiently strong to introduce an important degree of bias in studies of sulfonylureas and MI risk, the overall impact of these associations is difficult to predict given that some of these bias the results towards the null and others, away from the null. Furthermore, the

potential confounders identified differed in their prognostic strength and prevalence. For example, smoking and income inadequacy were found to be strongly associated with receiving a sulfonylurea, but these factors are unlikely to introduce an important degree of bias since their prevalence is so low. Similarly, physical inactivity and obesity were also found to be strongly associated but the impact of these factors on the risk of MI are in opposite direction given that users of sulfonylurea were twice as likely to be physically inactive, but at least half as likely to be obese.

Indication bias, or confounding by indication, can arise from the informed selection or channelling of a specific drug or drug class on the basis of a certain characteristic (i.e., causal associations), or as a result of association by proxy (i.e., incidental associations). In our study, the association between sulfonylureas and obesity is most likely to be causal since metformin is known to be preferentially prescribed to obese individuals.[11] This selective prescribing results in the channelling of obese persons away from sulfonylureas. In contrast, education, income, smoking, and physical activity are not known to influence a physician's choice of one OHA over another. However, several of these factors are known to be correlated with obesity and as such, could introduce incidental exposure-confounder associations. This would explain why metformin users were also more likely to have less education and lower incomes. Interestingly, these incidental or proxy associations were of similar magnitude as that with obesity. On the other hand, it is important to note that the correlations between these factors diminish their independent contributions to the overall magnitude of the bias they introduce. The association between sulfonylureas and smoking is not likely to be causal, nor is it easily explained by correlations since smoking is known to be correlated with lower education and income, factors more frequent among metformin users. This association may be due to chance or unknown correlations.

The limitations of our study need to be considered. First, the cross-sectional nature of the NPHS data makes it difficult to establish the temporality of some of the associations that were observed. For example, metformin users reported being more obese but also more physically active. However, it is possible that these individuals increased

their level of physical activity after being prescribed an antidiabetic medication, in which case physical activity is not associated with treatment choice. In addition, cross-sectional data do not necessarily capture prevalent users of sulfonylureas and metformin. As such, it is difficult to ensure that users of these agents are comparable with regards to diabetes progression. Since sulfonylureas are used as first line therapy in over 75% of cases of type 2 diabetes,[17, 18] it is possible that in our study users of metformin had previously received a sulfonylurea and therefore, had more advanced diabetes. This may, in part, explain the finding of more heart disease among users of metformin. Second, information on self-reported health and lifestyle may be of concern for a number of reasons. Respondents may be unwilling to divulge this information or may not understand or forget their diagnosis. However, the response rate to individual questions on the NPHS is very high and studies have reported excellent agreement between self-report and medical record diagnosis.[19-22] Consequently, the effect of misclassification is likely to be small and similar across treatment groups. Third, our ability to assess the distribution of risk factors across treatment groups was limited by the small number of users of sulfonylureas or metformin, as evidenced by the wide confidence intervals for several interesting estimates. Nonetheless, the magnitudes of the observed associations are certainly within the range of what would be expected. The small sample size also accounts for our inability to assess the joint distributions of potential confounders. Finally, our results may not be generalizable to other populations and jurisdictions given that prescribing behaviours are likely to be influenced by both of these factors.

In conclusion, we identified several potential sources of indication bias that will need to be accounted for in future observational studies of oral hypoglycemics and the risk of MI. In addition, a number of these sources of potential bias were not identified *a priori*, thereby highlighting the importance of incidental exposure-confounder associations. The overall impact of these sources of bias on the validity of such studies is difficult to assess qualitatively given that individual exposure-confounder associations differed in magnitude and direction. Consequently, a quantitative assessment of potential sources of indication bias will need to be undertaken.

DISCLAIMER

This study is based on non-identifiable data provided by Statistics Canada. The interpretation and conclusions contained herein do not necessarily represent those of the Government of Canada or Statistics Canada.

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Table 5.1. Prevalence of potential confounders measured in health databases

Determinants of health outcomes	Prevalence (P_C) †
Socio-economic status	
Low education (≤ high school)	0.59
Low income (< $15,000)	0.20
Health and lifestyle factors	
Poor health status (self-perceived)	0.11
Current smoking	0.14
Regular alcohol consumption	0.38
Obesity (BMI ≥ 30)	0.36
Regular physical activity	0.50

† Among survey respondents who were taking sulfonylureas or metformin

Table 5.2. Comparison of demographics and socio-economic status of individuals prescribed sulfonylureas and metformin

Characteristic [†]	Sulfonylureas (n=731)	Metformin (n=187)	Crude Odds Ratio (95% CI) [‡]	Age and sex adjusted Odds Ratio (95% CI) [‡]
Age (%) [*]				
< 60 years	24.8	47.0	1.00 (reference)	1.00 (reference)
≥ 60 years	75.2	53.0	2.69 (1.29-5.62)	2.68 (1.27-5.57)
Sex (%) [*]				
Female	42.5	44.0	1.00 (reference)	1.00 (reference)
Male	57.5	56.0	1.06 (0.45-2.48)	0.91 (0.39-2.13)
Place of residence (%) [*]				
Rural	19.6	28.6	1.00 (reference)	1.00 (reference)
Urban	80.4	71.4	1.64 (0.55-4.82)	1.92 (0.65-5.64)
Highest level of education (%) [*]				
> high school	42.4	36.0	1.00 (reference)	1.00 (reference)
≤ high school	57.6	64.0	0.76 (0.34-1.72)	0.63 (0.27-1.49)
Labour status (%) [*]				
Not working in past year	73.7	68.0	1.00 (reference)	1.00 (reference)
Working in past year	26.3	32.0	0.76 (0.30-1.93)	0.61 (0.22-1.72)
Income (%) [*]				
Moderate to high income	82.5	68.3	1.00 (reference)	1.00 (reference)
Low income	17.5	31.7	0.46 (0.15-1.35)	0.34 (0.11-1.04)

[†] Among individuals who responded to the question pertaining to a particular characteristic. Non-respondents included those who were not eligible to answer a particular question (e.g., labour status and children), did not understand or misinterpreted a question, could not recall, or refused to answer. Ineligibility to answer a particular question was the major reason for missing information.

[‡] Variances calculated using sampling weights provided by Statistics Canada and the bootstrap re-sampling method to derive exact variances for individuals. Age (years) modeled as a continuous variable.

[*] Weighted using sampling weights provided by Statistics Canada to account for multi-stage sampling strategy.

Table 5.3. Comparison of the clinical profiles of individuals prescribed sulfonylureas and metformin

Characteristic [†]	Sulfonylureas (n=731)	Metformin (n=187)	Crude Odds Ratio (95% CI) [‡]	Age and sex adjusted Odds Ratio (95% CI) [‡]
Co-morbid conditions (%) *				
Hypertension	48.5	47.1	1.06 (0.47-2.38)	0.80 (0.35-1.81)
Heart disease	20.7	29.6	0.62 (0.26-1.45)	0.47 (0.20-1.12)
Cerebrovascular disease	5.0	4.5	1.13 (0.14-8.87)	0.93 (0.12-7.50)
Respiratory illness	8.9	7.8	1.56 (0.40-3.31)	1.23 (0.40-3.77)
Arthritis and rheumatism	46.5	34.9	1.62 (0.75-3.52)	1.13 (0.50-2.53)
Gastrointestinal ulcers	4.9	0.79	6.44 (1.27-32.68)	7.02 (1.18-41.87)
Crohn's / ulcerative colitis	1.7	4.4	0.38 (0.00-56.24)	0.52 (0.00-90.09)
Thyroid disorder	6.0	5.9	1.02 (0.28-3.7)	1.19 (0.20-7.04)
Cataracts or glaucoma	16.2	4.5	4.1 (1.25-13.34)	2.36 (0.70-7.96)
Use of concomitant drugs (%) *				
Blood pressure pills	51.7	47.2	1.19 (0.54-2.62)	0.82 (0.35-1.90)
Diuretics	13.2	17.4	0.72 (0.23-2.19)	0.70 (0.18-2.73)
Heart medication	19.6	31.2	0.54 (0.22-1.33)	0.36 (0.14-0.92)
Asthma medication	6.7	4.8	1.41 (0.24-8.19)	1.39 (0.22-8.87)
Corticosteroids	1.2	1.1	1.10 (0.00-600)	***
Stomach medication	7.3	5.7	1.29 (0.47-3.55)	1.22 (0.40-3.66)
Thyroid medication	6.5	5.8	1.12 (0.32-4.04)	2.15 (0.31-14.80)
Health services utilization [¶]				
Hospitalizations (%) *				
None	79.2	84.0	1.00 (reference)	1.00 (reference)
≥ 1	20.8	16.0	1.38 (0.39-4.87)	1.12 (0.32-3.84)
Physician services (%) *				
Family physician visits				
< 1 per month	78.3	65.6	1.00 (reference)	1.00 (reference)
≥ 1 per month	21.7	34.4	0.53 (0.24-1.15)	0.48 (0.21-1.12
Eye specialist (%)*				
None	38.1	35.4	1.00 (reference)	1.00 (reference)
≥ 1	61.9	64.6	0.89 (0.39-2.05)	0.77 (0.33-1.76)

[†] Among individuals who responded to the question pertaining to a particular characteristic. Non-respondents included those who were not eligible to answer a particular question (e.g., labour status and children), did not understand or misinterpreted a question, could not recall, or refused to answer. Ineligibility to answer a particular question was the major reason for missing information.

[‡] Variances calculated using sampling weights provided by Statistics Canada and the bootstrap re-sampling method to derive exact variances for individuals. Age (years) modeled as a continuous variable.

* Weighted using sampling weights provided by Statistics Canada to account for multi-stage sampling strategy.

[§] Among female respondents only.

[¶] In the year preceding the interview.

*** Unstable or could not be estimated.

Table 5.4. Comparison of the health and lifestyle profiles of individuals prescribed sulfonylureas and metformin

Characteristic [†]	Sulfonylureas (n=731)	Metformin (n=187)	Crude Odds Ratio (95% CI) [‡]	Age and sex adjusted Odds Ratio (95% CI) [‡]
Health and lifestyle				
Self-perceived health status (%) [*]				
Very good to excellent	23.4	21.0	1.12 (0.47-6.65)	1.05 (0.44-2.48)
Fair to good	66.2	66.4	1.00 (reference)	1.00 (reference)
Poor	10.4	12.6	0.82 (0.27-2.52)	0.82 (0.20-3.32)
Smoking status (%) [*]				
Never smoked	37.6	39.4	1.00 (reference)	1.00 (reference)
Ever smoked	62.4	60.6	1.08 (0.48-2.41)	1.09 (0.44-2.71)
Never smoked	37.6	39.4	1.00 (reference)	1.00 (reference)
Current smoker	15.0	8.4	1.86 (0.60-5.78)	2.79 (0.79-9.83)
Past smoker	47.4	52.2	0.95 (0.40-2.24)	0.84 (0.79-9.83)
Alcohol consumption (%) [*]				
Abstainer	13.4	17.1	1.00 (reference)	1.00 (reference)
Former drinker	27.1	29.5	1.16 (0.31-4.43)	1.03 (0.24-4.44)
Occasional drinker	18.6	30.8	0.77 (0.20-2.99)	0.98 (0.22-4.35)
Regular drinker	40.9	22.6	2.30 (0.62-8.55)	2.91 (0.69-12.27)
Body Mass Index (BMI) (%) [*]				
< 30	66.0	60.3	1.00 (reference)	1.00 (reference)
≥ 30	34.0	39.7	0.78 (0.24-2.56)	0.67 (0.20-2.22)
Physical activity (%) [*]				
Infrequent	40.1	24.5	1.00 (reference)	1.00 (reference)
Occasional	11.3	20.5	0.33 (0.11-1.05)	0.42 (0.11-1.54)
Regular	48.6	55.0	0.54 (0.23-1.25)	0.77 (0.31-1.92)

[†] Among individuals who responded to the question pertaining to a particular characteristic. Non-respondents included those who were not eligible to answer a particular question (e.g., labour status and children), did not understand or misinterpreted a question, could not recall, or refused to answer. Ineligibility to answer a particular question was the major reason for missing information.
[‡] Variances calculated using sampling weights provided by Statistics Canada and the bootstrap re-sampling method to derive exact variances for individuals. Age (years) modeled as a continuous variable.
[*] Weighted using sampling weights provided by Statistics Canada to account for multi-stage sampling strategy.

5.3 Additional discussion

In this study we assessed the potential for residual confounding due to unmeasured risk factors in a database study of the effect of OHAs on MI risk by evaluating the distribution of these unmeasured factors, obtained from an external data source, across exposure groups, and quantifying the strength of these exposure-risk factor associations.

We used the National Population Health Survey (NPHS) for the current study because it is the largest survey of its kind in Canada and was expected to be representative of the prescribing trends of physicians in Saskatchewan, at least with regards to the unmeasured risk factors of interest. Unfortunately, this data source had several limitations, the most important being the small numbers of individuals actually treated with an OHA. This combined with Statistics Canada's policy of suppressing information for cell counts of 30 or less, yielded extremely unstable estimates of the associations of interest. In addition, the limited sample size also prevented us from assessing the correlation between unmeasured risk factors. Finally, at the time the current study was carried out, the NPHS did not capture information on thiazolidinediones, an exposure of primary interest in the main study. The ideal source of data for assessing indication bias in the main study would have been a survey of a sub-sample of the original study population. However, our hypothesis of confounding by calendar time and the need to survey at different point in time, together with the extended calendar period (1978-2001) covered by the main study, rendered such a survey unfeasible.

In the current study, we observed important differences between users of sulfonylureas (an exposure of interest) and metformin (reference group) with regards to income, level of education, smoking status, alcohol consumption, physical activity and obsesity. However, the strength and direction of the sulfonylurea-smoking association was unexpected and counterintuitive. In general, individuals who are obese also tend to be of lower socio-economic status and have a lower level of education and physicial activity. The latter factors are also known to be correlated with smoking status. In other

words, we would have expected that users of metformin would have been more likely to be smokers, as these individuals were more obese, had a lower level of education and income. Instead, we found that users of sulfonylureas were more likely to be smokers. As discussed in the manuscript, the latter association may have occurred by chance or secondary to unknown correlations with other factors. The sulfonylurea-smoking association requires confirmation in other data sources.

The overall impact, in terms of magnitude and direction of residual confounding, of the observed associations are difficult to predict qualitatively given that this will be influenced by the magnitude and direction of individual associations as well as by the prevalence of the unmeasured risk factor in the population. Consequently, in the next chapter we develop a simulation-based tool to quantify and correct the observed associations in the main study for the sources of residual bias observed in the current study.

CHAPTER 6: QUANTIFYING AND CORRECTING RESIDUAL CONFOUNDING

6.1 Preface to the manuscript

This chapter contains the final manuscript in a series of three articles on the postmarketing safety evaluation of the oral hypoglycemic agents (OHAs). In the previous study, we demonstrated the potential for residual confounding due to unmeasured risk factors in an observational database study of the effect of OHAs on the risk of myocardial infarction (MI). This source of bias threatens the validity of the findings of the main study particularly since the overall magnitude and direction of residual confounding is difficult to predict.

In the study presented here, we develop an approach for quantifying and correcting for the presence of residual confounding due to unmeasured risk factors observed in the previous study using information from external data sources. While the concept of "external adjustment" to correct for residual confounding is not new, the simulation-based approach developed here provides researchers with a unique tool that is easy to implement. In addition, to correcting for confounding by indication due to unmeasured confounders, this tool can also be used for predicting the size of the association that would be needed to explain an observed association. The simulation-based tool also enabled us to study the behaviour of this bias and determine the factors that influence its magnitude and direction.

We used data from several, readily available sources of information to develop the simulation-based tool including from the main study for information on the apparent odds ratio for the OHA-MI association and the prevalence of the exposure of interest in the source population; published studies of the determinants of MI risk for information on the strength and direction of the outcome-confounder odds ratio; and empirical estimates of the exposure-confounder relationships, as well as the prevalence of the confounder from the National Population Health Survey (NPHS) of Canada used in the previous study.

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6.2 Quantifying and correcting confounding by indication bias due to unmeasured risk factors: a simulation-based approach

QUANTIFYING AND CORRECTING CONFOUNDING BY INDICATION BIAS DUE TO UNMEASURED RISK FACTORS: A SIMULATION-BASED APPROACH

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ABSTRACT

Background: Confounding due to unmeasured risk factors can be an important threat to the validity of observational studies of drug effects. As such, researchers require tools to assist them in quantifying the impact and direction of this potential source of bias in individual studies.

Objective: To develop a tool for quantifying and correcting for confounding by indication due to unmeasured risk factors and assess the behaviour of this bias.

Methods: We simulated an unmatched case-control study where exposure status and risk factors were assigned using a multinomial distribution conditioned on the outcome. To determine joint probabilities of these binary variables, we assigned the prevalence of exposure (P_E) and confounder (P_C), the exposure-confounder odds ratio (ECOR), the outcome-confounder odds ratio (OCOR), and the unadjusted or apparent exposure-outcome odds ratio (App OR). The latter was obtained from a previous study of the association between acute myocardial infarction and various oral hypoglycemic agents (OHAs). Joint probabilities were calculated for a variety of clinically plausible scenarios identified from external data sources. Using a 1:4 case-control ratio, we generated 1000 samples of 5000 individuals. From these samples, we estimated the "true" OR adjusted for the missing risk factor using logistic regression, and compared the "true" and apparent OR to derive the magnitude and direction of the bias. The simulation-based tool was used to adjust the OHA-MI risk estimate, observed in the previous study, for unmeasured risk factors.

Results: For situations typically encountered in pharmacoepidemiology studies of the unintended effects of drugs, the magnitude of confounding bias due to a single unmeasured risk factor is small. For example, failure to adjust for a potential confounder with a prognostic association representative of that of common unmeasured risk factors (OCOR=2.0), would introduce a bias of 5% if physicians preferentially prescribed the drug under study 50% more often than the comparator treatment (ECOR=1.5) in the presence of this risk factor, and a bias of 12% if the study drug was chosen twice as often

(ECOR=2.0). However, extreme situations, such as those encountered in studies of the known benefits of drugs, can lead to significant bias, particularly when the prevalence of the confounder is close to 50%. The direction of confounding by indication bias depends on the simultaneous influence of the OCOR and the ECOR.

Conclusions: This study demonstrates that the conditions required to introduce important bias due to residual confounding are not easily met in pharmacoepidemiologic studies of the unintended adverse effects of drugs, particularly in the context of known but unmeasured risk factors. In the example of the association between sulfonylureas and MI, our findings indicate that the interpretation of the risk estimate is unlikely to be materially affected on a number of important determinants of this outcome.

BACKGROUND

Observational studies have made significant contributions to our understanding of the risks and benefits associated with drug therapy. Indeed, pharmacoepidemiologic studies are often the first to identify or confirm the presence of important adverse health outcomes associated with the use of medications, as seen recently with the adverse cardiac effects of the cyclooxygenase-2 (COX-2) inhibitors [1-4] and certain anti-parkinsonian agents [5]. This type of study can also address aspects of drug safety and effectiveness that cannot be readily or adequately evaluated using an experimental design, including the time-varying nature of the risk [6] and the health benefits of drugs for important but rare outcomes [7, 8]. As such, pharmacoepidemiologic studies are necessary to compliment the information provided by randomised controlled trials.

Increasingly, pharmacoepidemiologic studies are conducted using administrative health care claims databases. This data source provides detailed information on prescription drug use, medical services and procedures, and hospitalizations, for large and unselected populations that are representative of those treated in routine practice. Moreover, these populations can be followed for extended periods of time in a cost and time efficient manner.[9] However, these databases typically lack information on some important determinants of health outcomes including socio-economic status, and health and lifestyle factors such as self-perceived health status, alcohol consumption, smoking status, body mass index (BMI), and physical activity. When one or more of these factors influences a physician's choice of treatment, that factor becomes independently associated with both the risk of the outcome and the probability of being exposed and as such, introduces confounding by indication bias.[10]

The possibility of residual confounding due to missing information on risk factors can be an important threat to the validity of pharmacoepidemiologic studies. The risk of acute myocardial infarction (MI) associated with the use of oral hypoglycemic agents (OHAs) is an example of this problem which has significant public health implications given the current epidemic of type 2 diabetes[11, 12] and the high baseline risk of cardiovascular morbidity and mortality in this population[13, 14]. While a recent meta-

analysis has raised important safety concerns about the adverse cardiac effects of a new class of OHAs, the thiazolidinediones, most of the trials reviewed were of short duration and powered to assess surrogate endpoints in relatively younger and healthier individuals than those commonly treated in routine practice.[15] Furthermore, concerns regarding the cardiotoxicity of the sulfonylureas, an older but popular class of OHAs, have not been adequately addressed by trials published to date. Pharmacoepidemiologic database studies can overcome many of these limitations, however, they are likely to be criticized for not being able to control for important unmeasured risk factors that could also be potential confounders.

Pharmacoepidemiologic studies usually provide a qualitative assessment of the potential for residual confounding based on informed assumptions about prescribing behaviours. However, few studies include a quantitative evaluation of the magnitude and direction of this bias. Approaches that have been proposed to quantitatively assess residual confounding include: (1) sensitivity analyses based on an array of informed assumptions about the distribution of the unmeasured factor across the exposure groups under study, the prevalence of the exposure in the source population, and the strength of the outcome-confounder association,[16, 17] (2) sensitivity analyses based on empirical measures of the aforementioned parameters,[16, 18] (3) determination of the strength of the exposure-confounder relationship required to explain the observed association,[16, 19] and (4) adjustment of the observed exposure-outcome estimate using information on the unmeasured risk factors obtained from an external source, such as a survey of a representative population or a sub-sample of the study population [17, 20, 21]. While it has been suggested that quantitative evaluations of residual confounding should replace qualitative ones,[22] few of the proposed methods have provided researchers with the tools necessary to readily implement these techniques.

In this paper, we first develop a simulation-based tool, based on established methods of external adjustment, to estimate the magnitude and direction of confounding due to a single unmeasured binary covariate, in the context of an unmatched case-control study, and to correct the observed estimate, in any given study, for residual confounding.

Next, we assess the behaviour of this bias over a broad range of clinically plausible scenarios, and follow with an illustration of the use of this tool using the example from a previous study of MI risk associated with the use of sulfonylureas and metformin; two of the most commonly prescribed OHAs.

METHODS

Data sources

For the development of the simulation-based tool, five parameters were pre-specified: (1) the observed exposure-outcome odds ratio not controlling for unmeasured risk factors, referred to as the *apparent odds ratio* (AOR), (2) the exposure-confounder odds ratio (ECOR), (3) the confounder-outcome odds ratio (OCOR), (4) the prevalence of the exposure (P_E) in the source population, and (5) the prevalence of the unmeasured risk factor in the source population (P_C). The values used for these parameters were based on informed assumptions about the range of clinically plausible values for each parameter, supplemented by a review of the medical literature (Table 6.1).

We used data from three sources to illustrate how to assess the overall impact of confounding bias due to unmeasured factors, and correct the observed estimate in a given study. First, we used the results of a matched case-control analysis of a cohort of individuals newly treated for type 2 diabetes, to obtain an estimate of the AOR for acute MI associated with the use of sulfonylureas compared with metformin.[23] Matched case-control data were used for simplicity given that they were available and that an unmatched analysis of these data had yielded similar results. This data source also provided an empirical estimate of P_E for sulfonylureas (obtained from the controls). Second, estimates of the OCOR for important risk factors that are typically unavailable in health databases were abstracted from studies of the determinants of acute MI published in the medical literature.[24-27] These risk factors included educational attainment, income, smoking, alcohol consumption, obesity, and physical activity. When literature estimates varied across studies, the strongest estimate (i.e., furthest from the null) was chosen. Third, empirical estimates of the ECOR and P_C for these potential confounders were obtained from a previous analysis of the 1996/97 Health file of the Canadian National

Population Health Survey (NPHS), undertaken to evaluate the distribution of determinants of adverse health events across individual OHAs and quantify the strength of the exposure-confounder associations for users of sulfonylureas compared with metformin.[28] Briefly, the NPHS is conducted every two years in a representative sample of over 58,000 Canadians and the Health file provides detailed information on self reported socio-demographics, medical conditions, medication use, health and lifestyle factors for 17,626 of the survey respondents.[29]

Simulation study

We simulated an unmatched case-control study comprised of 1000 cases and 4000 controls. For simplicity, we only considered the case where the exposure, confounder, and outcome were dichotomous variables, and accounted for a single unmeasured risk factor at a time. We assumed that the exposure, confounder and outcome were measured without error. The relationships between the exposure, potential confounder and the outcome, depicted in Figure 6.1, were used to derive the equations for the joint probabilities of exposure and confounder, conditioned on the outcome (Appendix 6.1). Assuming no effect modification, the relationship between the exposure and the confounder can be expressed as:

$$OR_{EC|D=1} = OR_{EC|D=0} \text{ or } p_1p_4/p_2p_3 = p_5p_8/p_6p_7$$

That is, the ECOR was assumed to be the same for cases and controls. In addition, since a confounder must be associated with the outcome independent of the exposure, the outcome-confounder relationship can be expressed as:

$$OR_{OC|E=1} = OR_{OC|E=0} \text{ or } p_1p_6/p_2p_5 = p_3p_8/p_4p_7$$

That is, the OCOR was taken to be the same for the exposed and unexposed group. Consequently, the observed or apparent OR (AOR) in any given study, unadjusted for an unmeasured risk factor, can be expressed as:

$$AOR = [(p_1+p_2)(p_7+p_8) / (p_5+p_6)(p_3+p_4)]$$

For each fixed combination of the AOR, ECOR, OCOR, P_E, and P_C (Table 6.1), cases and controls were assigned an exposure and confounder status in accordance with the joint probabilities calculated for cases (i.e., p_1-p_4) and controls (i.e., p_5-p_8) using a multinomial distribution. Once the dataset had been simulated, the crude exposure-outcome odds ratio (i.e., apparent OR) and the odds ratio adjusted for the presence of a single unmeasured risk factor (i.e., "externally adjusted" OR) were estimated using logistic regression. We generated 1000 case-control datasets for each scenario evaluated. Odds ratios presented in the results are geometric means of the OR from the 1000 simulations ($e^{[\text{mean }(\beta)]}$). The magnitude and direction of the bias was obtained by comparing the "externally adjusted" OR with the AOR and expressed as the percentage change in estimates ([(AOR – "externally adjusted" OR) / "externally adjusted" OR] *100%).

Empirical illustration

We used the tool developed in the simulation study, and the estimates for AOR, ECOR, OCOR, P_E, and P_C previously described, to generate 1000 case-control samples comprised of 4320 cases, as in the previous study,[23] and 86,400 controls using a 1:20 ratio. This step was repeated for each of the six unmeasured determinants of MI previously described. The age-and-sex adjusted ECORs for these potential confounders were stronger than the crude estimates for some factors (education, income, smoking, and alcohol consumption), but attenuated for others (obesity and physical activity). Consequently, we undertook the primary assessment of confounding bias using the adjusted estimates of ECOR, and repeated the simulations using the crude estimates. The magnitude and direction of residual confounding for the association between sulfonylureas and acute MI, reported in a previous study, was estimated separately for each of the potential confounders using the approach described in the simulation study. We also estimated the overall impact of residual confounding using two approaches. First, we used the method proposed by Schneeweiss and colleagues[30] and summed the bias estimates over all confounders, each weighted by the prevalence of the respective confounder. Second, we carried out a simple addition of the bias estimates since our simulation-based approach already accounted for the influence of P_C.

All analyses were performed using Statistical Analysis Software (SAS) version 9.1.3 for windows. The SAS macro for the simulation-based tool used in the illustration can be found in Appendix 6.2 .

RESULTS

We evaluated a total of 18,000 clinically plausible scenarios for the simulation study. Table 6.2 displays the results of a sample of the simulations for the association between a dichotomous exposure and outcome, in the context of assessing an unexpected adverse drug effect. For these scenarios, the apparent OR was set at 1.5, 2.0 and 3.0, the OCOR at 1.5 and 3.0 to represent moderate and strong risk factors, the ECOR at 1.5 and 2.0 to represent moderate and strong levels of selective prescribing, the P_E at 0.10 and 0.25 to represent common and high frequencies of exposure, and the P_C ranged from 0.10 to 0.5. For each combination of OCOR, ECOR, P_E, and P_C, the apparent OR obtained from the simulation, the OR adjusted for the unmeasured confounder, and the percentage (%) change in estimate (i.e., % bias) are shown. A number of important patterns of bias were observed. First, we found that for any given combination of ECOR, P_E, and P_C, the magnitude of confounding bias increased as the OCOR increased. For example, when AOR, ECOR, P_E, and P_C took on the value of 1.5, 1.5, 0.10, and 0.25 respectively, the bias increased from 4.03% to 10.05% as the strength of the outcome-confounder relationship increased from 1.5 to 3.0. Similarly, the bias increased from 4.03% to 6.78% when the ECOR increased from 1.5 to 2.0 for the same scenario. In contrast, the impact of the prevalence of the exposure (P_E) was less pronounced and in the opposite direction of that of the OCOR and ECOR. For example, we found that for any combination of OCOR, ECOR, and P_C, the bias was somewhat attenuated by increasing values of P_E but was not affected by the strength of the AOR. The pattern of bias observed with changing values of the prevalence of the confounder (P_C) was more complex than that of the other parameters, and hence, more difficult to predict. For OCOR = 1.5, the magnitude of the bias increased steadily as P_C approached 0.50. For example, when ECOR = 1.5 and P_E = 0.10, the extent of confounding increased from 2.12% to 3.71% and 4.03% as P_C increased from 0.10 to 0.25 and 0.5. However, the maximum value of the bias was reached sooner (i.e., P_C = 0.25) when the strength of the prognostic factor was stronger

(i.e., OCOR = 3.0). Finally, the magnitude of the observed or apparent OR (AOR) had negligible impact on the extent of the bias. For example, at the highest value of OCOR, ECOR, P_E and P_C (last line of table), the magnitude of residual confounding was 17.75%, 17.76%, and 17.93% for an AOR of 1.5, 2.0 and 3.0. On the other hand, in situations where the AOR represents an overestimation of the true risk, as was the case here, the clinical significance of the bias depended on the strength of this parameter. For example, for the AORs described above the corresponding adjusted exposure-outcome estimates were 1.28, 1.70 and 2.55. While there is little doubt that a 70% or 155% increase in the risk of any major health event would be considered clinically significant, there could be more uncertainty about the importance of a 28% risk increase.

The behaviour of confounding bias as a function of the simultaneous influence of three of the five parameters studied is shown in Figure 6.2 . As expected, regardless of the strength of the AOR, P_E and P_C, no bias could be introduced by an unmeasured confounder when either OCOR or ECOR was equal to 1.0 (Figures 6.2a-h). However, the degree of confounding increased with increasing values of either association (Figures 6.2a and 6.2e). We also found that the value of P_C required to attain maximum confounding, increased as P_E increased (Figures 6.2d and 6.2h). For most of the scenarios studied, the bias did not reach the 10% change in estimate threshold for confounding.[31] However, when both the OCOR and ECOR were strong, the bias consistently exceeded the 10% threshold, particularly as P_C approached 0.5 (Figures 6.2d and 6.2h). As previously discussed, the bias behaved similarly for different values of the AOR: this can be seen by comparing the corresponding graphs for AOR = 1.5 and AOR = 3.0 .

In the scenarios depicted in Table 6.2, the apparent ORs were biased away from the null (i.e., overestimation of "true" risk) because both the OCOR and ECOR took on values of > 1.0. However, no generalizability is lost by only presenting these scenarios, as the extent for the corresponding reciprocal values of OCOR and ECOR below 1.0 would be the same. For example, the magnitude and direction of the bias when OCOR = 3.0 and ECOR = 2.0 would be the same as that for OCOR = 0.33 and ECOR = 0.5. Similarly, the magnitude and direction of the bias can be easily obtained when either OCOR or ECOR

is < 1.0 . As can be seen in Figure 5.3, for any given value of OCOR > 1.0, the magnitude of the bias for ECOR = 0.6 is the same as that for ECOR = 1.8, but in the opposite direction.

The results of the quantitative assessment of residual confounding on the validity of the risk estimate obtained from a previous study of sulfonylurea use and MI risk are shown in Table 6.3. We found that the inability to control for the potentially biasing effects of education, income, smoking, alcohol consumption, obesity and physical activity in the previous study resulted in a negligible underestimation of the association between the use of sulfonylureas and the risk of MI when each factor was considered separately. The overall magnitude of the bias was -0.37% using the simple sum method and -2.50% when weighted by the prevalence of each confounder. Smoking status was the strongest uncontrolled confounder resulting in 25.31% overestimation of the risk which, assuming independent effect of the confounders, appears to be largely was offset by an 11.90%, 7.47% and 4.89% underestimation of the risk due to unmeasured income, level of education, and obesity respectively. The extent of residual bias for the simple sum was higher (-11.42%) with the use of crude estimates of ECOR but essential unchanged for the weighted sum approach (-1.07).

DISCUSSION

This simulation study demonstrates that the conditions required to introduce an important degree of residual confounding due to known but unmeasured risk factors are not easily met in pharmacoepidemiologic studies of the unintended adverse effects of drugs. This is in part due to the importance of the exposure-confounder relationship in determining the overall impact of residual bias and the lower potential for such associations in these studies. For example, strong causal exposure-confounder associations, such as selective prescribing and drug channelling, are less likely to be present in studies where the outcome is unintended. Incidental exposure-confounder associations can be introduced when the determinants of the unintended effect are correlated with those related to the indication for the treatment. However, such associations are expected to be weaker than causal ones. The simulation also indicates

that while the direction of residual confounding due to a single unmeasured confounder is easy to predict, this is not necessarily true when several potential confounders are unmeasured, as individual sources of bias may be in opposite direction. Furthermore, the magnitude of overall residual bias cannot be estimated qualitatively as it depends on the joint contributions of the strength and direction of the outcome-confounder and confounder-exposure associations, and the prevalence of the exposure and confounder in the source population.

In the example of the relationship between sulfonylureas and MI, our findings indicate that the interpretation of the risk estimate appears largely unaffected by the lack of information on a number of important determinants of this outcome when each factor is considered independently. This is largely due to the fact that the overall magnitude of the bias introduced by these unmeasured confounders appears to be negligible and towards the null despite important confounding by some of these factors. Both the unadjusted and externally adjusted estimates suggest a small risk increase for sulfonylurea use that warrants further investigation. On the other hand, the strong association with smoking is worrisome as external adjustment for this factor eliminated the association between sulfonylureas and MI.

We made several simplifying assumptions that may have affected the extent of residual confounding. First, we assumed no effect modification by the unmeasured risk factors. While this assumption cannot be empirically verified, it is nonetheless reasonable. Second, we only considered the case where the exposure, confounder, and outcome were dichotomous variables. While this is appropriate for the MI outcome and the exposure of interest (sulfonylurea vs. metformin), the cutpoints chosen for continuous risk factors could have an impact on the strength of the exposure-confounder association and the prevalence of this factor. On the other hand, the cutpoints used in our analysis were chosen to correspond with those identified in studies assessing the prognostic strength (OCOR) of individual risk factors. Third, both of the methods used to calculate the overall magnitude of residual confounding assumed that the unmeasured risk factors were independent of one another and independent of measured confounders. However, many of

these factors are known to be correlated (e.g., obesity, education, smoking, and income). When individual sources of bias are in the same direction, it has been suggested that this assumption would lead to an overestimation of the overall extent of the bias.[30, 32] This may not be the case in our study because individual sources of bias are in opposite directions. For example, since education and income are known to be highly correlated, it is conceivable that most of the residual bias could be explained by income alone. If this were the case, the overall extent of the bias would be towards the null (i.e., positive). Although the overall impact of these unmeasured correlations is difficult to predict, it seems unlikely that the association between sulfonylureas and MI would disappear altogether given that the highly correlated risk factors considered here are also known to be independent determinants of MI. Lastly, we assumed that confounders were measured without error. As this is unlikely to be the case in a database study, the resulting confounder misclassification would have reduced our ability to control for confounding.[33, 34]

The assessment of residual confounding using external data sources depends of the validity, completeness, and representativity of these data. We used the strongest outcome-confounder associations reported in the literature to minimize the potential for residual confounding. Data from the NPHS, used to estimate the exposure-confounder associations and the prevalence of unmeasured confounders, have been shown to have a high rate of completeness for individual questions, and studies have reported excellent agreement between self-reports and medical records diagnoses.[35-38] The use of external data sources does not account for the potentially biasing effects of unknown risk factors. However, it is unlikely that such a factor would be strong enough to change our interpretation of the risk of MI associated with the use of sulfonylureas, given that the determinants of MI identified to date account for at least 90% of the risk.[26] Despite these limitations, the simulation-based assessment of the impact and direction of residual confounding proposed in this study is superior to the qualitative assessments that are typically undertaken.

Similar to other techniques that have been proposed,[22] our simulation-based approach only addresses the simple case of a single dichotomous confounder. As such, further work is needed to extend the univariable external adjustment method presented here, to the more realistic case of multiple unmeasured confounders. Recently, Sturmer and colleagues proposed a multivariable approach to external adjustment using propensity score calibration.[39] Although this technique appears very promising, it has yet to be validated.

The inability to control for the potentially biasing effects of some important risk factors is a common criticism of observational studies using administrative health databases. The simulation-based approach proposed in this study allows researchers to quantify the overall extent and direction of residual confounding and correct the observed exposure-outcome association within the limits of the assumptions of this technique and the quality of the external data used. Our analysis demonstrates that the inability to adjust for six important potential confounders is unlikely to significantly bias the association between sulfonylurea use and the risk of MI.

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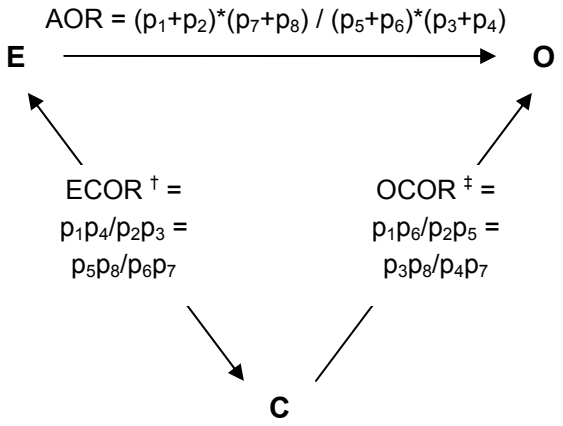
Table 6.1 Values of the parameters used in the simulations of the unmatched case-control study populations

Parameter	Abbreviation	Range of values
Apparent Odds Ratio †	AOR	0.5 to 2.0 by 0.25, 2.5, 3.0, 4.0
Exposure-confounder Odds Ratio	ECOR	0.25 to 2.0 by 0.25
Outcome-confounder Odds Ratio ‡	OCOR	0.5 to 2.0 by 0.25, 2.5, 3.0
Prevalence of the exposure under study §	P_E	0.1, 0.25, 0.5, 0.75, 0.9
Prevalence of the unmeasured confounder §	P_C	0.1, 0.25, 0.5, 0.75, 0.9

† Observed in a specific study but unadjusted for unmeasured risk factors.
‡ Independent effect of the risk factor for the outcome under study.
§ In the source population.



Among Cases

	C = 1	C = 0
E = 1	P_1	P_2
E = 0	P_3	P_4

Among Controls

	C = 1	C = 0
E = 1	P_5	P_6
E = 0	P_7	P_8

Figure 6.1 Relationships between the exposure, confounder and outcome

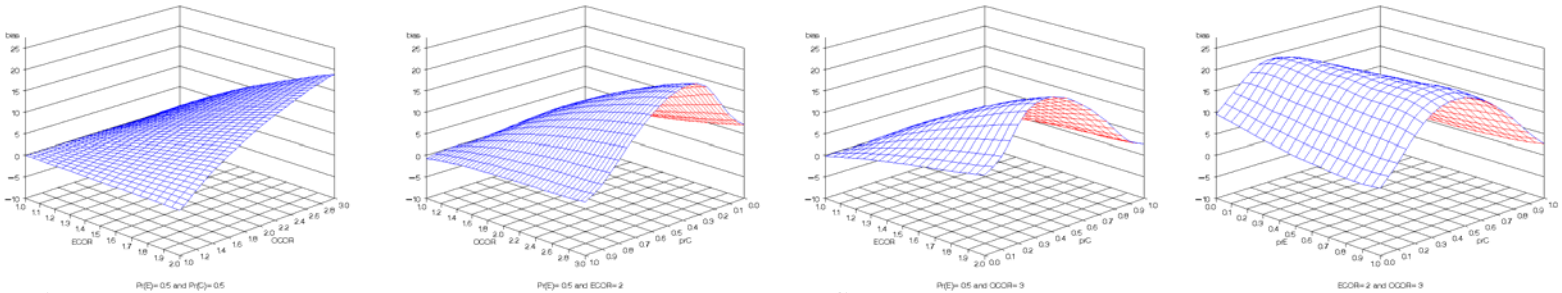
† Assuming no effect modification, ECOR (cases) = ECOR (controls).
‡ By definition OCOR (exposed) = OCOR (unexposed) since a confounder must be associated with the outcome independent of the exposure.

Table 6.2 Magnitude of confounding bias due to a single unmeasured dichotomous variable for a sample of clinically plausible scenarios

Apparent Odds Ratio = 1.5							Apparent Odds Ratio = 2.0							Apparent Odds Ratio = 3.0						
OCOR†	ECOR†	P_E	P_C	AOR‡	OR	% Bias	OCOR†	ECOR†	P_E	P_C	AOR‡	OR	% Bias	OCOR†	ECOR†	P_E	P_C	AOR‡	OR	% Bias
1.5	1.5	0.10	0.10	1.51	1.48	2.12	1.5	1.5	0.10	0.10	1.99	1.95	1.91	1.5	1.5	0.10	0.10	3.00	2.94	1.96
1.5	1.5	0.10	0.25	1.51	1.45	3.71	1.5	1.5	0.10	0.25	2.00	1.93	3.66	1.5	1.5	0.10	0.25	2.99	2.88	3.63
1.5	1.5	0.10	0.5	1.50	1.44	4.03	1.5	1.5	0.10	0.5	2.00	1.92	4.03	1.5	1.5	0.10	0.5	2.99	2.88	4.00
1.5	1.5	0.25	0.10	1.49	1.46	1.94	1.5	1.5	0.25	0.10	2.00	1.97	1.92	1.5	1.5	0.25	0.10	2.99	2.94	1.85
1.5	1.5	0.25	0.25	1.49	1.44	3.55	1.5	1.5	0.25	0.25	2.00	1.93	3.56	1.5	1.5	0.25	0.25	2.99	2.89	3.58
1.5	1.5	0.25	0.5	1.50	1.45	4.07	1.5	1.5	0.25	0.5	2.01	1.93	4.07	1.5	1.5	0.25	0.5	3.00	2.89	4.04
1.5	2.0	0.10	0.10	1.49	1.44	3.63	1.5	2.0	0.10	0.10	2.00	1.93	3.72	1.5	2.0	0.10	0.10	3.00	2.89	3.64
1.5	2.0	0.10	0.25	1.50	1.40	6.50	1.5	2.0	0.10	0.25	2.00	1.88	6.43	1.5	2.0	0.10	0.25	2.99	2.80	6.53
1.5	2.0	0.10	0.5	1.51	1.41	6.78	1.5	2.0	0.10	0.5	2.01	1.88	6.79	1.5	2.0	0.10	0.5	3.01	2.82	6.76
1.5	2.0	0.25	0.10	1.50	1.45	3.38	1.5	2.0	0.25	0.10	2.00	1.94	3.32	1.5	2.0	0.25	0.10	3.00	2.90	3.38
1.5	2.0	0.25	0.25	1.50	1.41	6.28	1.5	2.0	0.25	0.25	2.00	1.88	6.19	1.5	2.0	0.25	0.25	3.00	2.82	6.19
1.5	2.0	0.25	0.5	1.49	1.39	6.93	1.5	2.0	0.25	0.5	1.99	1.86	6.92	1.5	2.0	0.25	0.5	3.01	2.81	6.89
3.0	1.5	0.10	0.10	1.49	1.40	6.66	3.0	1.5	0.10	0.10	2.00	1.87	6.84	3.0	1.5	0.10	0.10	2.99	2.80	6.94
3.0	1.5	0.10	0.25	1.49	1.34	11.15	3.0	1.5	0.10	0.25	2.00	1.80	11.07	3.0	1.5	0.10	0.25	3.00	2.71	10.90
3.0	1.5	0.10	0.5	1.51	1.37	10.05	3.0	1.5	0.10	0.5	2.00	1.81	10.15	3.0	1.5	0.10	0.5	3.00	2.72	10.19
3.0	1.5	0.25	0.10	1.50	1.40	6.62	3.0	1.5	0.25	0.10	2.00	1.87	6.68	3.0	1.5	0.25	0.10	2.99	2.81	6.61
3.0	1.5	0.25	0.25	1.50	1.35	10.93	3.0	1.5	0.25	0.25	2.00	1.81	10.85	3.0	1.5	0.25	0.25	3.01	2.71	10.88
3.0	1.5	0.25	0.5	1.50	1.36	10.36	3.0	1.5	0.25	0.5	2.00	1.81	10.29	3.0	1.5	0.25	0.5	3.00	2.72	10.23
3.0	2.0	0.10	0.10	1.49	1.32	13.03	3.0	2.0	0.10	0.10	2.00	1.77	12.89	3.0	2.0	0.10	0.10	2.99	2.65	12.84
3.0	2.0	0.10	0.25	1.50	1.25	19.74	3.0	2.0	0.10	0.25	2.02	1.68	19.81	3.0	2.0	0.10	0.25	3.00	2.50	20.15
3.0	2.0	0.10	0.5	1.50	1.28	17.16	3.0	2.0	0.10	0.5	1.99	1.70	17.22	3.0	2.0	0.10	0.5	3.01	2.57	17.10
3.0	2.0	0.25	0.10	1.50	1.34	11.97	3.0	2.0	0.25	0.10	2.00	1.79	11.93	3.0	2.0	0.25	0.10	3.01	2.68	12.06
3.0	2.0	0.25	0.25	1.50	1.25	19.41	3.0	2.0	0.25	0.25	2.00	1.68	19.44	3.0	2.0	0.25	0.25	3.00	2.52	19.36
3.0	2.0	0.25	0.5	1.50	1.28	17.75	3.0	2.0	0.25	0.5	2.01	1.70	17.76	3.0	2.0	0.25	0.5	3.00	2.55	17.93

OCOR = Outcome-confounder Odds Ratio; ECOR = Exposure-confounder Odds Ratio; PE = Prevalence of the exposure in the source population; PC = prevalence of the confounder in the source population; AOR = Apparent Odds Ratio observed in a given study, not controlling for the unmeasured confounder; OR = Odds Ratio externally adjusted for the unmeasured confounder.
† Rounded to one decimal place for simplicity but in reality there is a small variation introduced by the simulation. The magnitude of this variation is similar to that depicted for the AOR.
‡ There is a small variation introduced by the simulation between the pre-specified value of AOR and that calculated by the simulation.

Apparent OR=1.5



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Apparent OR = 3.0

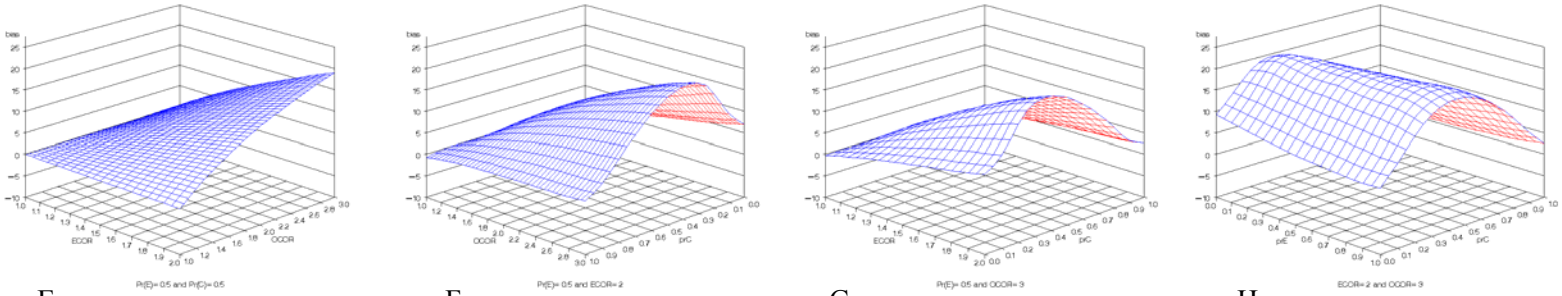

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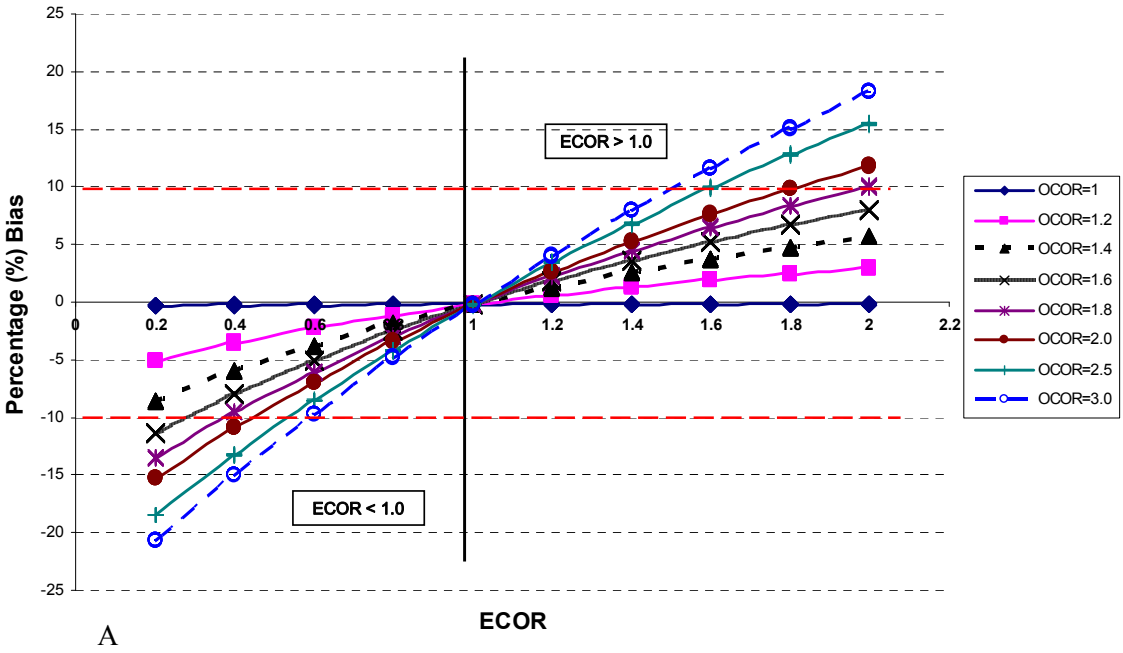
Figure 6.2 Magnitude and direction of residual confounding from simulations of a study of the unintended adverse effect of a drug.



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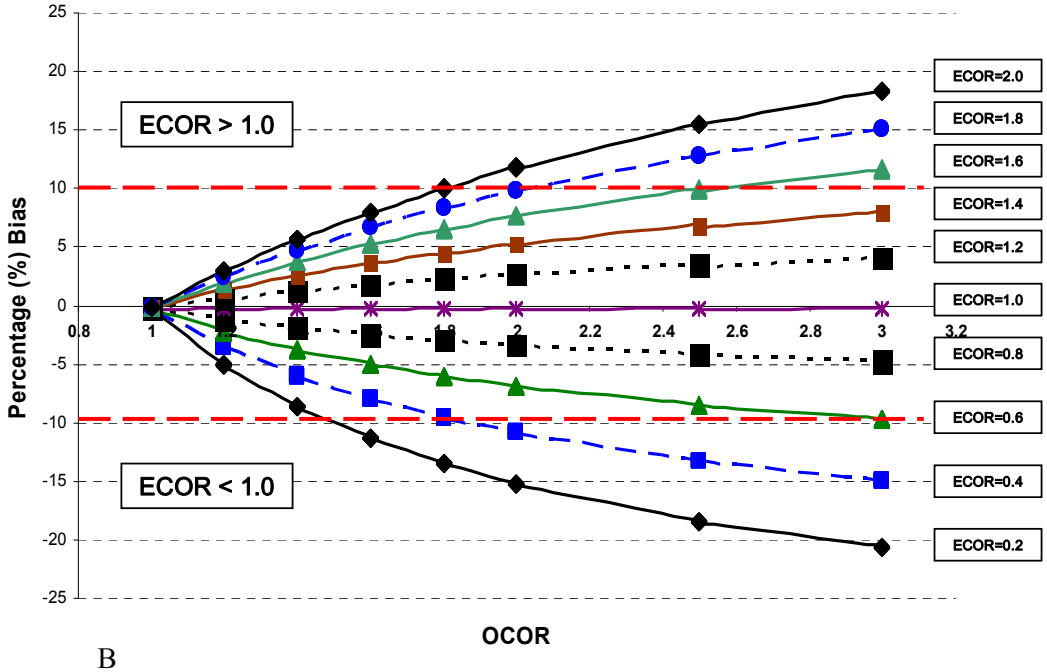

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Figure 6.3 Residual confounding as a function of the OCOR and ECOR

Table 6.3 Quantitative assessment of residual confounding for the association between current use of sulfonylureas and acute myocardial infarction

Unmeasured risk factor	OCOR	ECOR†	P_E ‡	P_C §	Apparent OR *	Externally adjusted OR‖	% Bias ¶	Weighted % Bias ¶
Education (≤ high school vs. > high school)	2.10 ¥	0.63	0.18	0.59	1.24	1.34	- 7.47	- 2.03
Income (< $15,000 vs ≥ $ 15,000)	2.10 £	0.34	0.18	0.20	1.24	1.41	- 11.90	- 1.10
Smoking (current vs. never)	3.10 #	2.79	0.18	0.14	1.24	0.99	+ 25.31	+ 1.63
Alcohol consumption (regular vs. abstainer)	0.91 #	2.91	0.18	0.38	1.24	1.27	- 2.40	- 0.42
Obesity (BMI > 27 vs. ≤ 27)	1.70 &	0.67	0.18	0.36	1.24	1.30	- 4.89	- 0.81
Physical activity (regular vs. infrequent)	0.86 #	0.77	0.18	0.50	1.24	1.23	+ 0.98	+ 0.23
Sum of all negative biases							- 26.66	- 4.36
Sum of all positive biases							+ 26.29	+ 1.86
Overall extent of residual confounding							- 0.37	- 2.51

OCOR = Outcome-confounder Odds Ratio; ECOR = Exposure-confounder Odds Ratio; P_E = prevalence of exposure in source population; P_C = prevalence of potential confounder in source population; BMI = body mass index.
† From an analysis of the Canadian National Population Health Survey (NPHS). Age-and-sex adjusted OR for having the risk factor for sulfonylurea vs. metformin.[28]
‡ Prevalence of current use of sulfonylurea among controls obtained from a study of OHAs and MI risk.[23]
§ Prevalence of potential confounders from an analysis of the Canadian National Population Health Survey (NPHS).[28]
* Apparent odds ratio for acute myocardial infarction associated with use of sulfonylureas compared with metformin, not controlling for the unmeasured risk factor.[23]
‖ Odds ratio for acute myocardial infarction associated with use of sulfonylureas compared with metformin, adjusted for the influence of the unmeasured risk factor.
¶ Bias = [(Apparent OR – Externally corrected OR") / Externally corrected OR] * 100. A minus (-) indicates that the observed or apparent OR was an underestimation of the true OR, while a plus (+) indicates that the observed or apparent OR was an overestimation of the true OR.
¥ From the WHO MONICA study of men and women <65 years.[24]
£ From the Kuopio Ischemic Heart Disease Risk Factor Study.[25]
From the INTERHEART study of men and women from 52 countries with median ages of 51-63.[26] The OCORs used are those fully adjusted for other risk factors. This study and others have reported that the effect of smoking is significantly lower in those ≥65 years (OR = 2.44).
& From the SHEEP study combining the estimate for men (relative risk [RR] = 1.90) and women (RR = 1.50).[27]

Appendix 6.1 Derivation of the equations for the joint probability of the exposure and confounder conditioned on the outcome

From figure 1 we know that:

1. $p_5+p_6=P_E$
2. $p_5+p_7=P_C$
3. $p_5+p_6+p_7+p_8=1$
4. $p_5p_8/(p_6p_7)=ECOR_{(controls)}$

We also have:

5. $(p_1+p_2)(p_7+p_8)/[(p_3+p_4)(p_5+p_6)]=AOR$
6. $(p_1p_6)/(p_2p_5)=OCOR$
7. $p_1+p_2+p_3+p_4=1$
8. $(p_1p_4)/(p_2p_3)=ECOR_{(cases)}$

If ECOR, P_E, and P_c are fixed then p_5 to p_8 can be expressed as function of ECOR, P_E, P_c.

$p_6=P_E-p_5$

$p_7=P_c-p_5$

$p_8=1-P_E-P_C+p_5$

and $p_5 = \dfrac{[1+(ECOR-1)(P_E-P_C)]-\sqrt{[1+(ECOR-1)(P_E-P_C)]^2-4(ECOR-1)P_EP_CECOR}}{2(ECOR-1)}$

If AOR and OCOR are also fixed, expressions for p_1 to p_4 depends only on known parameters.

$$p_1 = \frac{p_5 OCOR \dfrac{P_E AOR}{1+P_E(AOR-1)}}{P_E + p_5(OCOR-1)}$$

$$p_2 = \frac{P_E AOR}{1+P_E(AOR-1)} - p_1$$

$$p_3 = \frac{p_1(1-p_1-p_2)}{p_2 ECOR + p_1}$$

$p_4=1-p_1-p_2-p_3$

Appendix 6.2 SAS Macro for simulation-based assessment and correction of residual confounding due to unmeasured risk factors

```
%put &sysdate9;

/*****************************************************************
* TITLE:     simulation                                          *
* OBJECTIVE: To evaluate the impact of a single binary           *
*            confounder on the exposure-outcome association      *
*            in an unmatched case-control analysis.              *
*****************************************************************/

options nodate nonumber nonotes;


/*Results of the simulation will be put in a file in the SAS data library
referred by the libname lib. */

/*"SAS-data-library" must be change to a valid path pointing to the directory
where the result will be save.*/
/*Enclose the path name in quotation marks.*/
/*EX: libname lib "C:\Documents and Settings\All Users\Desktop*/
libname lib "SAS-data-library";

/*Change the word filename by the name of the SAS dataset in which the results
will be saved*/
/*Must be a valid SAS name. (See SAS documentation for more details)*/
%let result=filename;

/*Setting the values necessary to the simulation*/

%let numberofsample=10; /*number of sample to be use, must be >0*/
%let number_ctrl=4; /*number of control for each case, must be >0*/
%let number_case=10; /*number of case in the study, must be >0*/
%let AOR_value=1.5; /*apparent OR, must be >0*/
%let OCOR_value=1.5; /*OCOR value, must be >0*/
%let ECOR_value=1.5; /*ECOR value, must be >0*/
%let prob_exp=0.5; /*probability of exposure in source population, must be
between 0 and 1*/

/*One of the two next probability MUST be missing, the other must be between 0
and 1*/
%let prob_confounder=0.5; /*probability of presence of confounder in source
population*/
%let prob_conf_exp=.; /*probability of presence of confounder AND exposure in
source population*/

/*************************************************************************
**
                        NO CHANGE NEEDED BELOW THIS LINE!
*************************************************************************
*/

/*Macro definition*/
%macro simulation(nsim=1000, ratio=4, ncase=10,
                  app_OR=1, OCOR=1, ECOR=0.5,
                  prE=0.5, prC=0.1, prEC=.);
proc datasets nolist; delete donnees prob test: res est:; run;
%put app_OR=&app_OR, OCOR=&OCOR, ECOR=&ECOR, prE=&prE, prC=&prC, prEC=&prEC;
/*validity check*/
%if %sysevalf(&ECOR<=0) or %sysevalf(OCOR<=0) or %sysevalf(&prE<=0) or
```

```
      %sysevalf(&prE>=1) or %sysevalf(&app_OR<=0) or %sysevalf(&nsim<=0) or
      %sysevalf(&ratio<=0) or %sysevalf(&ncase<1) %then %do;
      %put ERROR in supplied parameters;
            %goto exit;
%end;
%if (%sysevalf(&prC=.) and (%sysevalf(&prEC<=0) or %sysevalf(&prEC>=1) or
      %sysevalf(&prEC>=&prE))) or
      (%sysevalf(&prEC=.) and (%sysevalf(&prC<=0) or %sysevalf(&prC>=1))) or
      (%sysevalf(&prC ne .) and %sysevalf(&prEC ne .)) %then %do;
            %put ERROR in supplied parameters;
      %goto exit;
%end;
/*probabilities calculation from ECOR, OCOR, AOR, PrE, PrC (or PrEC)*/
data prob;
 /*
 p00=Pr(E=1|D=0);
 p01=Pr(E=1|D=1);
 p1=pr(E=1,C=1|D=1)
 p2=pr(E=1,C=0|D=1)
 p3=pr(E=0,C=1|D=1)
 p4=pr(E=0,C=0|D=1)
 p5=pr(E=1,C=1|D=0)
 p6=pr(E=1,C=0|D=0)
 p7=pr(E=0,C=1|D=0)
 p8=pr(E=0,C=0|D=0)
 (E,C|D=1) is multinomial(ncase, p1,p2,p3,p4)
 (E,C|D=0) is multinomial(ncontrol, p5,p6,p7,p8)

 Confounding: OR(EC|D=1)=OR(EC|D=0) therefore
 ECOR=OR(EC|D=1)=(p1*p4)/(p2*p3)=(p5*p8)/(p6*p7)=OR(EC|D=0)
 Risk factor independant of exposure:
 OCOR=OR(CD|E=1)=(p1*p6)/(p2*p5)=(p3*p8)/(p4*p7)=OR(DC|E=0)

 We also have:
 p1+p2+p3+p4=1
 p5+p6+p7+p8=1
 p1+p2=p01
 p5+p6=p00
 */
 p00=&prE;
 p01=1/(1+(1-p00)/(&app_OR*p00));
 a=(&ECOR-1);
 b=-(1+(&ECOR-1)*p00+(&ECOR-1)*&prC);
 c=&ECOR*p00*&prC;
 if %sysevalf(&prEC ne .) then do; p5=&prEC; p7=(1-p00)*p5/(&ECOR*(p00-p5)+p5);
end;
 if %sysevalf(&prC ne .) then do; p5=(-b-sqrt(b*b-4*a*c))/(2*a); p7=&prC-p5;
end;
 p1=p01*&OCOR*p5/(&OCOR*p5+p00-p5);
 p2=p01-p1;
 p3=(1-p01)*p1/(&ECOR*(p01-p1)+p1);
 p4=1-p01-p3;
 p6=p00-p5;
 p8=1-p00-p7;
 call symput('prob1',trim(left(p1)));
 call symput('prob2',trim(left(p2)));
 call symput('prob3',trim(left(p3)));
 call symput('prob4',trim(left(p4)));
 call symput('prob5',trim(left(p5)));
 call symput('prob6',trim(left(p6)));
 call symput('prob7',trim(left(p7)));
 call symput('prob8',trim(left(p8)));
run;
```

```
 /*data generation*/
 /*validity check*/
 %if %sysevalf(&prob1>0) and %sysevalf(&prob2>0) and %sysevalf(&prob3>0) and
       %sysevalf(&prob4>0) and
       %sysevalf(&prob5>0) and %sysevalf(&prob6>0)  and %sysevalf(&prob7>0) and
       %sysevalf(&prob8>0) and
       %sysevalf(&prob1<1) and %sysevalf(&prob2<1) and %sysevalf(&prob3<1) and
       %sysevalf(&prob4<1) and
       %sysevalf(&prob5<1) and %sysevalf(&prob6<1) and %sysevalf(&prob7<1) and
       %sysevalf(&prob8<1) %then %do;
        data donnees; set prob;
         do nb=1 to &nsim;
              nbech=nb;
              seed=int(nb*%sysfunc(time()));
              do i=1 to %eval((&ratio+1)*&ncase);
                    if i<=&ncase then outcome=1;
                    else outcome=0;
                    if outcome=1 then call rantbl(seed,of p1-p4,gr);
/*multinomial (p1,p2,p3,p4) for case*/
                    else call rantbl(seed,of p5-p8,gr); /*multinomial
(p1,p2,p3,p4) for controls*/
                    if gr=1 then do; exposure=1; confounder=1; end;
                    if gr=2 then do; exposure=1; confounder=0; end;
                    if gr=3 then do; exposure=0; confounder=1; end;
                    if gr=4 then do; exposure=0; confounder=0; end;
                    output;
              end;
         end;
         drop i;
        run;
       /*logistic regression w/o adjustment for confounder: result should be
near AOR*/
       proc logistic data=donnees descending outest=est noprint;
        model outcome=exposure;
        by nbech;
       run;
       /*convergence problem*/
       proc freq noprint data=est; table _status_ / out=test; run;
       data _null_; set test; by _status_;
        retain problem 1;
        if index(_status_,'Converged') and count=&nsim then problem=0;
        if last._status_ then do;
              if problem=1 then call symput('problem1','YES');
              else call symput('problem1','NO') ;
        end;
       run;
       /*logistic regression with adjustment for confounder variable: result is
the expected "truth"*/
       proc logistic data=donnees descending outest=estadj noprint;
        model outcome=exposure confounder;
        by nbech;
       run;
       /*convergence problem*/
       proc freq noprint data=estadj; table _status_ / out=test; run;
       data _null_; set test; by _status_;
        retain problem 1;
        if index(_status_,'Converged') and count=&nsim then problem=0;
        if last._status_ then do;
              if problem=1 then call symput('problem2','YES');
              else call symput('problem2','NO') ;
        end;
       run;
       /*If no convergence problem detected*/
```

```
      %if &problem1=NO and &problem2=NO %then %do;
            proc univariate noprint vardef=n data=est;
             var exposure;
             output out=test1 mean=m std=s;
            run;
            proc univariate noprint vardef=n data=estadj;
             var exposure confounder;
             output out=test2 mean=m1 m2 std=s1 s2;
            run;
            data res;
             merge test1 test2;
             sim=&nsim; ECOR=&ECOR; OCOR=&OCOR;
             apparent_OR=&app_OR;
             prE=&prE; prEC=&prEC; prC=&prC;
             ncase=&ncase;
             ncontrol=&ncase*&ratio;
             array or40 or_crude or_adj or_conf;
             array moy40 m m1 m2;
             array sd40 s s1 s2;
             array lci40 lci_crude lci_adj lci_conf;
             array uci40 uci_crude uci_adj uci_conf;
             do i=1 to 3;
                    or{i}=exp(moy{i});
                    lci{i}=exp(moy{i}-1.96*sd{i});
                    uci{i}=exp(moy{i}+1.96*sd{i});
             end;
             drop i;
            run;
            proc append base=lib.&result data=res; run;
      %end;
      %else %do;
            %put CONVERGENCE PROBLEMS:;
            %put app_OR=&app_OR, OCOR=&OCOR, ECOR=&ECOR, prE=&prE, prC=&prC,
prEC=&prEC;
            %goto exit;
      %end;
 %end;
 %else %do;
      %put erreur: app_OR=&app_OR, OCOR=&OCOR, ECOR=&ECOR, prE=&prE, prC=&prC,
prEC=&prEC;
      %put p1=&prob1, p2=&prob2, p3=&prob3, p4=&prob4, p5=&prob5, p6=&prob6,
p7=&prob7, p8=&prob8;
      %goto exit;
 %end;
 %exit:
%mend simulation;

/*macro invocation;*/
%simulation(nsim=&numberofsample, ratio=&number_ctrl, ncase=&number_case,
                        app_OR=&AOR_value, OCOR=&OCOR_value,
ECOR=&ECOR_value, prE=&prob_exp,
                        prC=&prob_confounder, prEC=&prob_conf_exp);
```

6.3 Additional discussion

In this study we demonstrated that our inability to adjust for six important potential confounders that were unmeasured in the main study was unlikely to significantly bias the association between sulfonylurea use and the risk of MI. Unfortunately, we could not carry out a similar sensitivity analysis for TZD use as we did not have information on the strength and direction of potential TZD-confounder associations.

As discussed in the manuscript there were several important assumptions made in carrying out the external adjustment for the sulfonylurea-MI association that need to be carefully considered. The validity of this type of sensitivity analysis is very much dependent on the quality of the data from external sources.

CHAPTER 7: IMMORTAL TIME BIAS IN COHORT STUDIES

7.1 Preface to the manuscript

This chapter contains the fourth and final manuscript of this thesis. The current manuscript also addresses the issue of bias in observational studies of pharmacological interventions in type 2 diabetes. However, unlike the previous three articles, the current manuscript deals with the issue of the choice of analysis as a source of potential bias rather than with residual confounding bias.

In the study presented here, we address the issue of immortal time bias in a separate study of cholesterol lowering "statins" and diabetes progression. Using the cohort of newly treated individuals with type 2 diabetes from the main study, we identify a sub-cohort of only those individuals who entered the cohort on sulfonylureas or metformin between 1991 and 1996 to duplicate a previously published study and demonstrate the extent to which immortal time bias accounted for the previously reported protective effect of "statins" on diabetes progression.

This article will be submitted for publication and should be references as follows:

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7.2 Immortal time bias in an observational study of the progression of type 2 diabetes

IMMORTAL TIME BIAS IN AN OBSERVATIONAL STUDY OF THE PROGRESSION OF TYPE 2 DIABETES

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ABSTRACT

Background: A recent observational study reported that the use of HMG Co-A reductase inhibitors ('statins') delays the progression to insulin therapy in type 2 diabetes. However, the design and analysis of this study may have introduced immortal time bias.

Objective: To assess the extent to which immortal time bias accounted for the protective association between statins and the initiation of insulin by replicating the study.

Methods: We identified a population-based cohort of individuals, age 30 and over, newly treated with an oral hypoglycemic agent between 1991 and 1996, using the same Saskatchewan Health data as the previously published study. As was done in the previous study, users of lipid lowering drugs from 3 years before to 6 months after cohort entry were excluded. Statin exposure was equally defined as at least 1 year of use and the study outcome was the start of insulin therapy. To demonstrate and quantify immortal time bias, we replicated the time-fixed, intent-to-treat analysis used in the previous study to estimate the association between statin use and start of insulin, and compared it with a simple time-dependent approach that correctly classified follow-up time as "non-user" until the exposure definition was met and as "statin user" thereafter. These analyses were first carried out using Poisson regression to quantify the magnitude of immortal person-time and then using the Cox proportional hazards model.

Results: The cohort consisted of 11,661 persons with a mean age of 64.3 years and followed for an average of 4.9 years. Among these, 4.6% (n=532) met the definition of statin user and 12.2% (n=1,418) initiated therapy with insulin. In the time-fixed analysis, the immortal (and unexposed) period accounted for 68% of the person-time allocated to statin users and produced a crude rate ratio (RR) for starting insulin of 0.83 compared with non-users. In contrast, the time-dependent Poisson analysis that corrected for misclassified immortal time yielded a crude RR of 2.67. After adjusting for potential confounders, statin users appeared to be at lower risk than non-users of progressing to

insulin therapy in the time-fixed Cox analysis (RR, 0.74; 95% CI, 0.58-0.95), but not in the immortal time corrected Cox analysis (RR, 1.97; 95% CI, 1.53-2.52).

Conclusions: The use of statins was not found to delay the start of insulin therapy in those with newly treated type 2 diabetes once immortal time was accounted for in the analysis. The effect of statins on the progression of this disease remains uncertain.

BACKGROUND

Type 2 diabetes has reached epidemic proportions worldwide and as such, has become an important public health issue.[1-3] This chronic metabolic disorder, characterized by elevated blood glucose levels, is associated with a number of serious complications including blindness,[4] chronic renal failure,[5, 6] limb amputation,[7, 8] and cardiovascular disease[9, 10]. Diabetes-related complications are not only an important marker of disease progression, they are also major determinants of poorer prognosis.[10-12] It is therefore not surprising that a major focus of research in recent years has been the identification of interventions that delay the progression of this disease.

A recent observational study of individuals newly treated for type 2 diabetes reported that the use of HMG Co-A reductase inhibitors ('statins') delayed the progression to insulin therapy (adjusted hazard ratio [HR] 0.74, 95% confidence interval [CI] 0.56-0.97).[13] This is a surprising finding given that this association ought to be subject to confounding and would be expected to yield a HR > 1.0 as individuals whose diabetes progresses are more likely to develop cardiovascular disease, an indication for statins.[14, 15] However, the design and analysis of this study may have introduced immortal time bias.[16]

We replicated the previous study to demonstrate the presence of immortal time bias and assess the extent to which this bias accounted for the apparently protective association between statins and the initiation of insulin.

METHODS

Study population and data sources

The study population of adults newly treated for type 2 diabetes was identified using the same Saskatchewan Health databases as the previous study. These administrative databases, developed as a result of the universal health care programs of the province of Saskatchewan, Canada, have been described in detail elsewhere.[17] Briefly, these data sources provide comprehensive information on dates of coverage, socio-demographics, outpatient prescriptions, medical services and procedures, hospital

separation diagnoses and vital statistics for approximately 91% of residents (about one million people). The remainder have their health benefits covered by federal government agencies.

Study design

In accordance with the previous study, we identified a population-based cohort of all individuals, 30 years of age and older, newly treated with a sulfonylurea or metformin between January 1st, 1991 and December 31st, 1996. The date of their first oral hypoglycemic agent (OHA) prescription was taken as cohort entry. Individuals were excluded if they did not have at least one year of health coverage preceding cohort entry or had been dispensed an OHA or insulin during this one-year baseline period. As in the previous study, we identified new users of statins by excluding those who had received a lipid lowering agent from three years before to six months after cohort entry. The remaining individuals were followed until the earliest of the following exit dates: a first study outcome, end of coverage (due to death or emigration from the province), death, or end of study (December 31st, 1999).

Outcome

The study outcome, starting insulin therapy, was identified using the date of the first insulin prescription dispensed after cohort entry. Starting insulin was used as a surrogate marker of diabetes progression since the initiation of insulin in individuals treated with OHAs is likely to represent uncontrolled hyperglycemia due to disease progression.[18, 19] In accordance with the previous study, we excluded all individuals who initiated insulin before their first statin prescription.

Statin exposure

We identified all statin prescriptions dispensed after cohort entry. As was done in the previous study, cohort members were classified as "statin users" if there was at least one year between the date of their first and last statin prescription, otherwise they were considered "non-users".

Statistical analysis

To demonstrate and quantify the immortal time bias, we replicated the time-fixed, intent-to-treat analysis used in the previous study to estimate the association between the use of statins and the start of insulin therapy, and compared it with a simple time-dependent analysis that corrected for the misclassified immortal time.

In the time-fixed, intent-to-treat analysis, all person-days of follow-up between cohort entry and exit were classified as "exposed" for those who met the definition of statin users, regardless of the date on which they met the exposure definition, and as "unexposed" for non-users (Figure 7.1a). In the simple time-dependent analysis, person-days of follow-up were correctly classified as "unexposed" until the intended exposure definition of one year of use was met and as "exposed" thereafter (Figure 7.1b). These analyses were first carried out using Poisson regression to quantify the magnitude of misclassified immortal person-time and estimate the effect of statins on the need to initiate insulin therapy, and then using the Cox proportional hazards model.[20, 21] In the Cox model, the rate ratios, estimated from the hazard ratios, were adjusted for the potentially confounding effects of age, sex, a history of macrovascular disease, congestive hear failure and hypertension, and the concomitant use of aspirin, beta-blockers, nitrates, angiotensin converting enzyme (ACE) inhibitors, calcium channel blockers and diuretics, measured at baseline. In addition, two validated measures of health status, the chronic disease score (CDS)[22] and the number of distinct drugs dispensed,[23] were also used. All covariates were assessed in the year preceding cohort entry (baseline).

To asses the extent to which different sources of immortal time accounted for the protective association between statins and insulin initiation, we repeated the time-fixed and time-dependent analyses correcting cumulatively for each period of immortal time (Figure 7.2). The first period corresponded to the first 6 months of follow-up during which cohort members could not receive a statin by design. The second period was from the end of this exclusionary period until the date of the first statin prescription, and the

third period was the time needed, following the first statin prescription, to fulfil the intended "statin user" definition of at least one year of use.

Validation of the bias

To validate the presence of the immortal time bias, we repeated the identical study and analyses within the previously defined cohort of type 2 diabetes, first using nonsteroidal antiinflammatory drugs (NSAIDs) as the exposure of interest, then using gastric acid suppressive (GI) agents (H_2-receptor antagonists and proton pump inhibitors). These drugs were chosen because they are commonly prescribed to the elderly and have no known beneficial effect on the progression of type 2 diabetes and hence, the need to start insulin.

Ethics

The study was approved by the ethics review board of McGill University.

RESULTS

The cohort consisted of 11,661 adults newly treated with an OHA and followed for an average (SD) of 4.9 years (±2.3). The mean (SD) age at cohort entry was 64.3 years (±13.7) and 55% were male. In this population, 4.6% (n=532) met the definition of "statin users" (i.e., at least one year of use), while 4.5% (n=522) had received statins for less than one year and, in accordance with the previous study, were classified as "non-users". An additional 90.9% (n=10,607) were classified as non-users as they did not receive any statin prescriptions during follow-up. The mean time to first statin use was 3.1 years (±1.8) for statin users and 4.4 years (±2.0) for non-users who received at least one prescription. During follow-up, 1,418 individuals (12.2%) initiated therapy with insulin. As would be expected in a cohort of newly treated type 2 diabetes, the majority of these events occurred late in the follow-up (Figure 7.3). The overall number of events per 100 person-years was 2.1 (68/3221 person-years) for statin users, 2.9 (82/2859 person-years) for non-users who had received statins for less than one year, and 2.5 (1268/50,587 person-years) for never users.

The baseline characteristics of cohort members according to their use of statins are shown in Table 7.1. Statin users were younger than non-users, more likely to be male, and more likely to have a history of macrovascular disease and hypertension. They were also more likely to be using medications for cardiovascular disease in the year preceding cohort entry. On the other hand, statin users where less likely to have a history of congestive heart failure and had health status indicator scores similar to those of non-users.

In the time-fixed, intent-to-treat analysis that replicated the previous study, the immortal (and unexposed) period accounted for nearly 68% of the total person-time allocated to statin users and produced a crude rate ratio (RR) for starting insulin of 0.83 for statin use compared with non-use (Table 7.2). In contrast, the immortal time corrected crude RR was 2.67.

After adjusting for several potential confounders, statin users appeared to be at lower risk than non-users of progressing to insulin therapy in the time-fixed Cox analysis used in the previous study (RR, 0.74; 95% CI, 0.58-0.95), but not in the immortal time corrected Cox analysis (RR, 1.97; 95% CI, 1.53-2.52) (Table 7.3).

The extent to which different sources of immortal time accounted for the protective effect of statins observed in the previous study is shown in Table 7.4. The 26% reduction in the need to start insulin (RR, 0.74; 95% CI, 0.58-0.95) previously reported [1] was decreased to 18% (RR, 0.82; 95% CI, 0.64-1.05) after correcting for the first immortal period, and abolished after correcting for the second period (RR, 1.37; 95% CI, 1.07-1.76). The latter source of immortal time (i.e., from the end of the 6 month exclusionary period until the date of the first statin prescription) also represented the largest proportion of "non-use" person-time (42.7%) incorrectly allocated to "statin users" in the previous study, while the first and third immortal periods accounted for 8.3% and 16.5% respectively, of misclassified person-time.

Table 7.5 presents the results of the validation study using NSAIDs and GI drugs as the exposures of interest. When the time-fixed, intent-to-treat approach employed in the previous study was used to estimate the association between NSAIDs or GI drugs and the initiation of insulin, both treatments appeared to reduce the need for insulin (RR, 0.77; 95% CI, 0.62-0.96 and RR, 0.90; 95% CI, 0.72-1.13 for NSAIDs and GI drugs respectively) (Table 5). However, the protective effect disappeared after correcting for the misclassified immortal time using a time-dependent Cox analysis (RR, 1.45; 95% CI, 1.16-1.83 and RR, 1.84; 95% CI, 1.47-2.31 for NSAIDs and GI drugs respectively).

DISCUSSION

We have shown that the beneficial effect of statins on the progression of type 2 diabetes previously reported [13] can be ascribed to immortal time bias. After replicating the results of the previous study, we demonstrated that the use of statins did not delay the initiation of insulin therapy once immortal time was appropriately accounted for in the analysis. This finding is strengthened by the observed relationship between the decreasing magnitude of the protective effect of statins (from 0.74 to 1.97) and the increasing proportion of immortal and misclassified person-time corrected in sequential analyses (from 0 to 100%). Moreover, the presence of immortal time bias is corroborated by the observation that NSAIDs and GI drugs, agents not known to slow the progression of diabetes, can be made to appear protective when subjected to the same design and analysis as that of the previous study. The latter not only provides empiric evidence that the reported benefits of statins on diabetes progression were due to bias, it also demonstrates that the bias is the result of systematic error introduced by the design and analysis of the previous study and, therefore, is not specific to statins.

Immortal time refers to a period of follow-up in a cohort study during which, by design, the outcome under study cannot occur.[24, 25] Bias is introduced when this "immortality" advantage is associated with the exposure. In pharmacoepidemiology studies, this bias typically arises when the ascertainment of an individual's exposure status involves a delay or waiting period during which follow-up time is accrued.[16] In the statin and diabetes progression study previously published,[1] the time between cohort

entry and the fulfilment of the "statin user" definition is by design immortal and unexposed: immortal because those who enter the "statin user" cohort must be event free during the time period needed to satisfy the definition of "exposed", and unexposed because this period precedes the fulfilment of the intended "statin user" definition (i.e., at least one year of use). However in the time-fixed, intent-to-treat analysis used by the previous investigators, this immortal person-time, representing two-thirds of the total follow-up time for this group, was allocated to "statin users" rather than to "non-users". This misclassification of immortal time inadvertently inflated the denominator for "statin users", resulting in a spuriously low rate of events for this group compared to "non-users". For this reason, immortal time bias necessarily favours the exposed group, as shown with the analysis of NSAIDs and GI drugs. The corresponding period of follow-up for those who received <1 year of statin therapy was also immortal, however, this "unexposed" person-time was correctly allocated to non-users in the previous analysis and as such, did not contribute to the immortal time bias.

The bias characterized here has been previously described.[26-29] However, in the current analysis, we have shown that more complex designs can introduce new sources of immortal time that, in combination with an incorrect analysis, individually contribute to the magnitude of the bias. Indeed, three distinct sources of immortal time were studied and quantified: (i) an initial "no use of statins" exclusionary period during the first 6 months of follow-up, (ii) the time between the end of the exclusionary period and the date of the first statin prescription, and (iii) the one year period *after* the start of therapy needed to satisfy the intended "statin user" definition. We have also provided additional evidence of the direct relationship that exists between the duration of the immortal period and the magnitude of the bias. Unlike previous examples of this bias where the immortal period was short and events occurred early,[26, 27] the current analysis entailed a particularly long overall immortal period, due to the significant delay before the fulfilment of the "statin user" definition, and events that were also considerably delayed. This resulted in a significant distortion of the effect of statins on the progression of type 2 diabetes.

An increased awareness of immortal time bias is warranted given the frequency with which this bias is being observed, the wide variety of drug interventions and health outcomes that have been implicated, and the potential negative impact that such biased findings can have on clinical practice.[16] Several approaches have been proposed to avoid this bias including, using a time-dependent analysis such as that utilized in the current study,[26-28] studying only "survivors" of the immortal period by moving the start of follow-up (i.e., cohort entry) to the end of the immortal period,[25] and moving the start of follow-up for "users" to the date the exposure definition is met and for "non users" to a date assigned according to the distribution of the users' immortal time [30]. Alternatively, a nested-case control analysis of the cohort can be used.[31, 32] This approach has not only been shown to provide an unbiased estimate of the rate ratio that would be obtained from a traditional time-to-event analysis of the full cohort,[33, 34] its inherent time-dependent nature means that it is also free of immortal time bias.

Our study is likely also subject to bias, particularly confounding by indication. As diabetes progresses, individuals are more likely to develop cardiovascular disease, an indication for statins.[14, 15] By definition, those at higher risk of progressing are also considerably more likely to be prescribed a statin. Consequently, the statin-insulin association is inherently confounded. For this reason, our finding of a rate ratio of 1.97 for statin use in the immortal time corrected analysis should not be interpreted as evidence of an increased risk of progressing to insulin but rather, the result of residual confounding by indication; a source of bias which is difficult to resolve in observational studies of efficacy. Consequently, our objective was not to quantify the true nature of this association but rather, to demonstrate the presence of immortal time bias and delineate its impact on the previously reported statin-insulin association. As such, our results should not discourage the use of statins in those with newly treated type 2 diabetes, particularly given that diabetes itself is now considered an indication for the use of statins [18, 35]. Confounding by indication may also explain our observed rate ratios >1.0 for NSAIDs and GI drugs as individuals who progress and develop diabetic neuropathy and gastroparesis may be more likely to receive these agents to treat associated symptoms of pain and gastrointestinal discomfort.

The possibility of residual immortal time bias also needs to be considered. To remain true to the previous study's intended exposure definition of "at least one year of use",[13] we carried out our immortal time corrected, time-dependent analysis by classifying individuals as "non users" until the date on which they fulfilled this one year criteria and as "statin users" thereafter. The previous study operationalized this definition by evaluating the distance between the first and last statin prescription. Consequently, their approach could have introduced more immortal time than we corrected for in our analysis. However, there was no evidence of residual immortal time bias in our results, as demonstrated by the disappearance of the protective association. This is likely because very little of the mean 4.9 years of follow-up would have been left unaccounted for after an average wait of 3.1 years for the first statin prescription and an additional one year needed to fulfil the exposure definition.

Finally, the use of a simple dichotomous definition of exposure in the immortal time corrected, time-dependent analyses could have introduced misclassification bias. As previously mentioned, we assumed that individuals were exposed for the remainder of their follow-up once they had satisfied the "statin user" definition. However, it has been shown that long-term compliance with statins is low [36, 37] and because of this, these individuals may in fact have become "non users" later in their follow up. Consequently, later events may have been incorrectly allocated to "statin users" rather than to "non users". On the other hand, since the "non user" status was ascertained over the entire duration of follow-up, it is unlikely that it was misclassified. The long duration of follow-up and higher rate of events later on may have accentuated the impact of this differential misclassification. This may also explain, at least in part, why the associations studied were all >1.0 after correcting for immortal time bias.

In summary, we found that statins did not delay the start of insulin therapy in persons newly treated for type 2 diabetes once immortal time was accounted for in the analysis. Consequently, the results of the previous study cannot be taken as evidence that statins delay the progression of type 2 diabetes. The effect of statins on the progression of this disease remains uncertain.

DISCLAIMER

This study is based on non-identifiable data provided by the Saskatchewan Department of Health. The interpretation and conclusions contained herein do not necessarily represent those of the Government of Saskatchewan or the Saskatchewan Department of Health.

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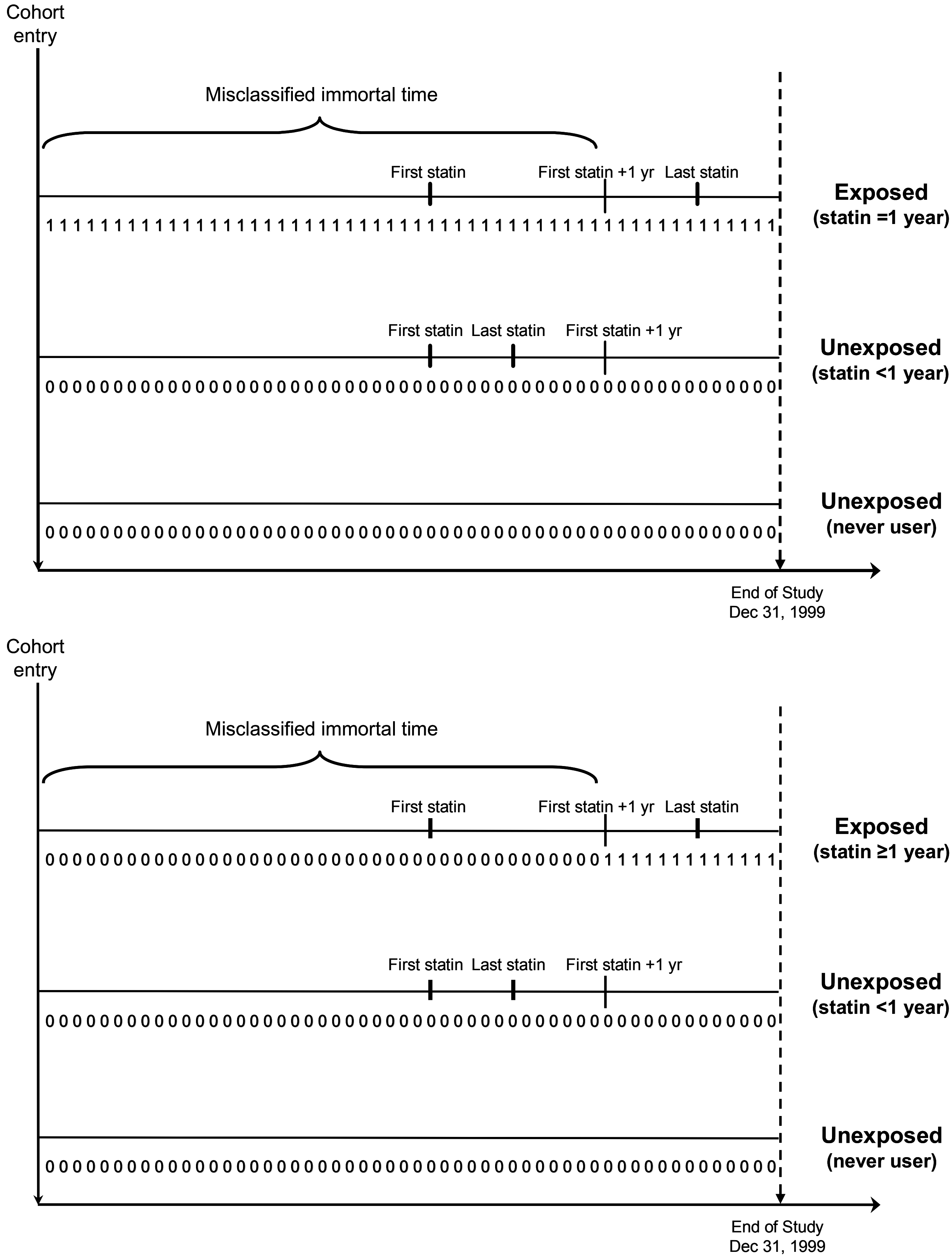

Figure 7.1 Depiction of typical statin user and non user in the cohort of newly treated type 2 diabetes. Statin use is a binary variable taking the value 1 for exposed person-days and 0 for unexposed person-days. In the time-fixed, intent-to-treat analysis used in the previous study (Figure A),[1] all person-days of follow-up were classified as exposed (1) for those who satisfied the "statin user" definition. However, in the time-dependent analysis (Figure B) used in the current study to correct misclassified immortal time, the person-days of follow-up were classified as unexposed (0) until the one year of use exposure definition was met, and as exposed (1) thereafter.

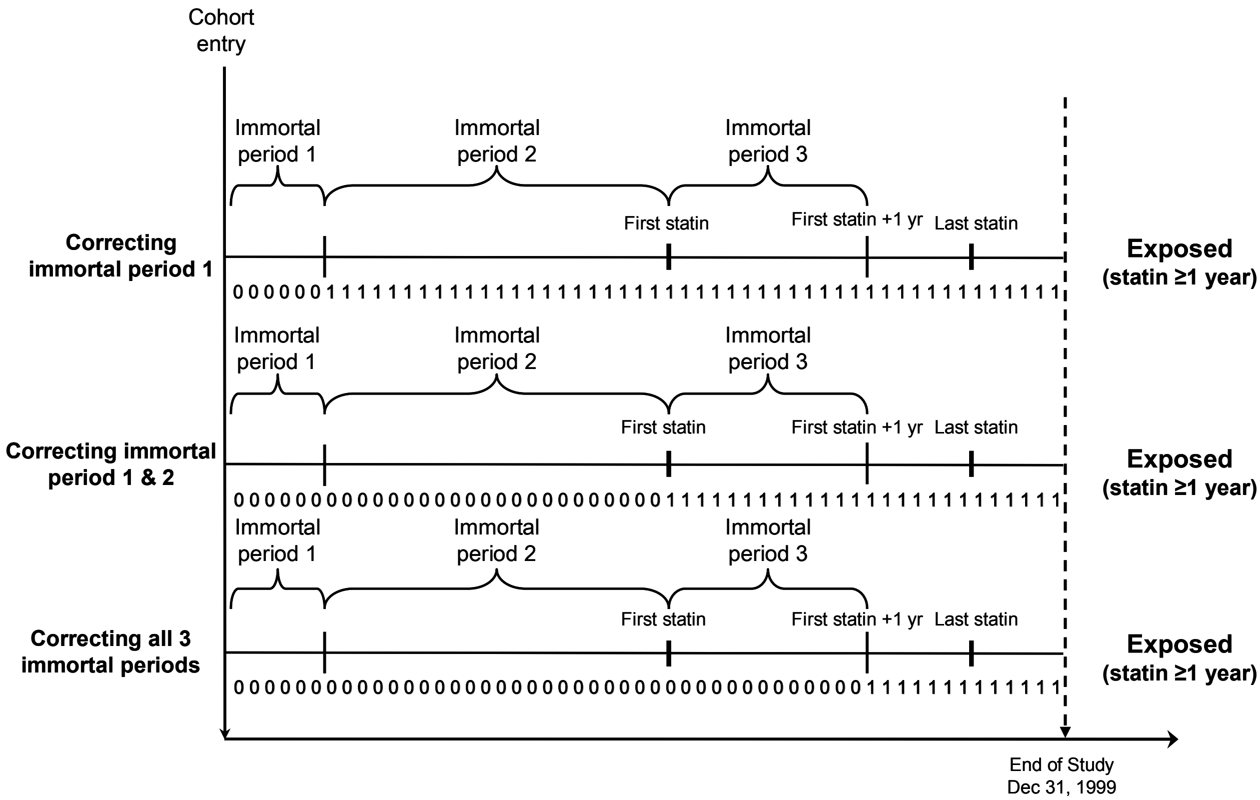

Figure 7.2 Sources of immortal time introduced by the design of the previous study [1] and the time-dependent analyses undertaken to correct each of these. Top: correcting immortal period 1 - the first 6 months of follow-up during which the use of statins was prohibited by design is immortal, since individuals had to survive this period to enter the cohort, and misclassified for those who became statin users since it precedes the exposure. This misclassified immortal period was corrected in the time-dependent analysis by classifying it as unexposed (0). Middle: correcting immortal period 2 - Similarly, the time between the end of this exclusionary phase and the first statin prescription was immortal and misclassified for statin users and was corrected using the approach described for period 1. Bottom: correcting immortal period 3 – the final source of immortal and misclassified person-time was the one year of use needed to fulfill the statin user definition. This was also corrected by classifying this follow-up time as unexposed (0).

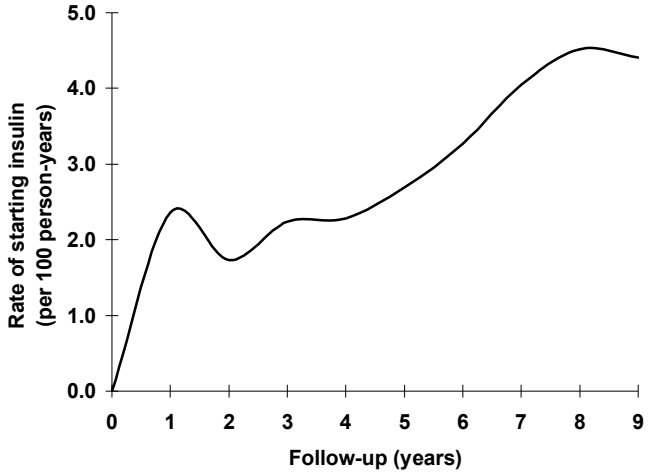

Figure 7.3 Rate of starting insulin as a function time since cohort entry

Table 7.1 Baseline characteristics of the study population according to the use of statin [†]

	Statin users (n = 532)	Non-users (n = 11,129)
Age, mean ± SD years [‡]	59.5 ± 9.7	64.5 ± 13.8
Male, n (%)	307 (57.7)	6129 (55.1)
Follow-up, mean (±SD) years	6.1 ± 1.8	4.8 ± 2.3
Comorbid conditions, n (%)		
Macrovascular disease [§]	100 (18.8)	1582 (14.2)
Congestive heart failure	23 (4.3)	1086 (9.8)
Hypertension	229 (43.0)	4183 (37.6)
Use of concomitant medications, n (%)		
Aspirin	39 (7.3)	631 (5.7)
Beta-blockers	100 (18.8)	1336 (12.0)
Nitrates	72 (13.5)	817 (7.4)
ACE-inhibitors	103 (19.4)	1733 (15.6)
Calcium channel blockers	107 (20.1)	1404 (12.6)
Diuretics	110 (20.7)	3251 (29.2)
Indices of health status		
Chronic Disease Score, mean ± SD	2.5 ± 2.8	2.4 ± 2.8
Number of unique drugs, mean ± SD	3.3 ± 2.9	3.3 ± 2.9

[†] In the year preceding cohort entry.
[‡] At cohort entry.
[§] Includes coronary artery disease, cerebrovascular disease and peripheral vascular disease.

Table 7.2 Distribution of person-time and events according to the use and non-use of statins before and after correcting for misclassified immortal time person-time

	Statin users			Non-users			
	Person-years	No. of Events †	Crude Rate ‡	Person-years	No. of Events †	Crude Rate ‡	Crude Rate Ratio §
Biased time-fixed analysis *							
Immortal person-time ¶	**2174**	0		0	0		
At-risk person-time	1046	68		53,446	1350		
Total person-time	3221	68	2.1	53,446	1350	2.5	0.83
Corrected time-dependent analysis							
Immortal person-time ¶	0	0		**2174**	0		
At-risk person-time	1046	68		53,446	1350		
Total person-time	1046	68	6.5	55,621	1350	2.4	2.67

† The event was starting insulin anytime after cohort entry.
‡ Rate of events per 100 person-years.
§ Assumes a constant rate of events over the duration of follow-up.
* Analysis used in the previously published study [1].
¶ Time from cohort entry until the day that the definition of "exposed" used in the previously published study was met.

Table 7.3 Crude and adjusted rate ratios for the initiation of insulin therapy associated with the use of statins before and after correcting for misclassified immortal time using Cox proportional hazards regression

	Number of Individuals	Number of Events †	Person-years	Crude RR	Adjusted RR ‡	95% CI
Biased time-fixed analysis §						
HMG-CoA reductase inhibitors (statins)						
Non-users (Reference)	11,129	1350	53,446	1.00	1.00	
Statin users	532	68	3,221	0.80	0.74	0.58-0.95
Corrected time-dependent analysis *						
HMG-CoA reductase inhibitors (statins)						
Non-users	11,129	1350	55,621	1.00	1.00	
Statin users	532	68	1046	2.15	1.97	1.53-2.52

Abbreviations: RR = Rate Ratio; CI = Confidence Interval.
† The study event was starting insulin anytime after cohort entry.
‡ Adjusted for age at cohort entry, sex, comorbid conditions, concomitant medications, and health status indicators listed in Table 1.
§ Analysis used in the previously published study.[1]
* Person-time of follow-up after cohort entry was correctly classified as “unexposed” until the day on which the definition of “exposed” was met.

Table 7.4 Impact of correcting for different sources of immortal time bias on the association between statin use and the start of insulin

Source of immortal time †	Immortal and misclassified person-time ‡ (years)	Immortal and misclassified time as a proportion of total exposed person-time §	Immortal period corrected using time-dependent analysis	Immortal and misclassified person-time corrected (years)	Proportion of immortal time bias corrected	Adjusted RR * (95% CI)
Periods 1 to 3	2174	67.5%	None	0	0%	0.74 (0.58-0.95)
Period 1	266	8.3%	1	266	12.2%	0.82 (0.64-1.05)
Period 2	1376	42.7%	1 and 2	1642	75.5%	1.37 (1.07-1.76)
Period 3	532	16.5%	1, 2 and 3	2174	100%	1.97 (1.53-2.52)

† Periods 1 to 3 = time from cohort entry to one year after the first statin prescription (i.e., all immortal person time included); Period 1 = time from cohort entry until 6 months later (i.e., period during which cohort members could not receive a statin); Period 2 = time from 6 months after cohort entry until the first statin prescription; Period 3 = time from the date of the first statin prescription to one year later (see Figure 2 for details).
‡ Classified as "exposed" in the previous study [1] even though this follow-up time preceded the fulfillment of the definition of "statin user".
§ Total person-time allocated to the "exposed" group (i.e., statin users) in the previous study is 3221 person-years (see Table 2 for details).
* Adjusted for age at cohort entry, sex, comorbid conditions, concomitant medications, and health status indicators listed in Table 1.

Table 7.5 Crude and adjusted rate ratios for the initiation of insulin therapy associated with the use of nonsteroidal antiinflammatory drugs and gastric acid suppressive drugs before and after correcting for misclassified immortal time using Cox proportional hazards regression

	Number of Individuals	Number of Events †	Person-years	Crude RR	Adjusted RR ‡	95% CI
Nonsteroidal antiinflammatory drugs (NSAIDs)						
Biased time-fixed analysis §						
Non-users (Reference)	5,902	706	27,390	1.00	1.00	
NSAID users	721	92	4,448	0.75	0.77	0.62-0.96
Corrected time-dependent analysis *						
Non-users (Reference)	5,902	706	28,935	1.00	1.00	
NSAID users	721	92	2903	1.42	1.45	1.16-1.83
Gastric acid suppressive agents (GI drugs)						
Biased time-fixed analysis §						
Non-users (Reference)	9,192	1,101	45,231	1.00	1.00	
GI drug users	643	87	3,967	0.85	0.90	0.72-1.13
Corrected time-dependent analysis *						
Non-users (Reference)	9,192	1,101	46,930	1.00	1.00	
GI drug users	643	87	2,268	1.76	1.84	1.47-2.31

Abbreviations: RR = Rate Ratio; CI = Confidence Interval.
† The study event was starting insulin anytime after cohort entry.
‡ Adjusted for age at cohort entry, sex, comorbid conditions, concomitant medications, and health status indicators listed in Table 1.
§ Analysis used in the previously published study.[1]
* Person-time of follow-up after cohort entry was correctly classified as “unexposed” until the day on which the definition of “exposed” was met

7.3 Additional discussion

In this study we demonstrated that the inappropriate accounting of person-time and exposure-status in the analysis of cohort studies can produce spuriously protective associations for a number of unrelated pharmacological interventions. This was brought about by the inappropriate choice of an intent-to-treat analysis when immortal time is present. Our results provided added justification for our choice of a nested case-control analysis in the main study.

CHAPTER 8: SUMMARY AND CONCLUSION

This thesis addressed bias related issues in the postmarketing evaluation of the cardiovascular safety of oral hypoglycemic agents. Specifically, we addressed a number of methodological challenges posed by studying the adverse effect of drugs in a disease that is typically prevalent at diagnosis and continues to progress over time. The biases specifically addressed in this thesis included confounding by diabetes duration, confounding by progression and severity, residual confounding due to unmeasured risk factors, and immortal time bias.

We found that the use of thiazolidinediones was associated with an increased risk of acute myocardial infarction and that the risk was apparent even in persons with no prior history of MI. Although we cannot rule out the possibility of residual confounding in this association, this is unlikely to completely explain the observed associations given that the risk for TZDs remained elevated regardless of the treatment group to which TZD users were compared, including insulin monotherapy.

We also found a small increased risk of MI for individuals currently exposed to sulfonylureas compared with metformin users, albeit much lower than that observed with TZDs. An external adjustment of the observed estimate for unmeasured confounders found that the risk increase was unlikely to be totally explained by this bias. It is important to note that the data used in the adjustment came from a different population and the estimates from these data were very imprecise given the small number of survey respondents that were taking oral hypoglycemic agents.

Our TZD results are consistent with those of three recent meta-analysis of rosiglitazone and MI risk. On the other hand, ours is the first population-based study to address the risk of MI associated with the use of sulfonylureas, as other studies evaluated cardiovascular death and all-cause mortality. In addition, our is the first observational study to address the important issue of confounding by diabetes duration and by progression and severity. Another important strength of this study was its use of a hard clinical end point to measure the impact of these medications. The vast majority of clinical trials published to date have used the surrogate end point of glycemic control.

On the other hand, pharmacoepidemiologic database studies are susceptible to confounding due to unmeasured risk factors. Our analysis of the NPHS data revealed some strong and unexpected associations between the use of specific OHAs and smoking. This risk factor is not known to influence physician prescribing of oral antidiabetics so it would be reasonable to assume that it was introduced by proxy. However, if this were the case, we would have expected that obese individuals who also are of lower income and education would be more likely to be smokers. In our study, the association was with users of sulfonylureas. This association requires confirmation given its magnitude.

Our study has some limitations that need to be considered. Cohort members were identified on the basis of the dispensing of an antihyperglycemic agent, including insulin. As such, it is possible that some cohort members had type 1 diabetes since administrative health data do not clearly distinguish between the two types. The impact of this is likely to be negligible because our of an age cut point of 35 years at treatment initiation would have eliminated most cases of types 1 diabetes including "Latent Autoimmune Diabetes in Adults". In addition, type 2 disease represents >90% of cases of diabetes among adults, particularly in a population newly treated at age 35 and over.

Selection bias is a major threat to the validity of observational studies as it is hard to detect and its influence cannot be controlled for in the analysis. In our study, the use of a relatively unselected, population-based cohort of new users of antihyperglycemics, combined with the use of a hard endpoint minimizes the potential for selection bias. Moreover, given the nature of administrative health data, losses to follow-up, another important source of selection bias, is very low and only occurs as a result of emigration from the province (i.e., termination of health coverage). In our study, losses to follow-up totalled 4.9% over a median follow-up of 6.8 years. One possible source of selection bias is incomplete ascertainment of outcomes due to missing information on silent MIs and out-of-hospital fatal MIs. If this occurs with equal frequency across treatment groups, the resulting misclassification would bias the results towards the null. Even if TZD or sulfonylurea use is more likely to induce silent MIs or fatal non-admitted MIs, the bias is still towards the null as "exposed" cases would be misclassified as "exposed" controls.

Misclassification of outcomes is unavoidable outside of the experimental setting, as misdiagnoses occur in clinical practice. However, if this occurs with equal frequency across treatment groups, the resulting misclassification would lead to an underestimation of the true risk. It is unlikely that detection bias explains our results, particularly with regards to our TZD findings since this risk had not been reported till recently. Indeed, the TZDs are marketed as being potentially cardioprotective on the basis of laboratory findings. Coding errors are possible in database studies. However, it has been shown that 96.9% of myocardial infarctions identified using hospital discharge diagnoses also appear in the medical record. Moreover, since the abstracting of diagnoses is carried out independent of the recording of exposure, any resulting misclassification would be non-differential.

In our main study, we used the Saskatchewan Prescription Drugs Database as a source of exposure information. This data source offers several advantages and some disadvantages. This database provide objective, accurate (within the limits of human error) and complete information on prescriptions dispensed to an individual, on an outpatient basis. The quality and completeness of this information (e.g., drug name, dosage, quantity dispensed) is expected to be at least as good as or better than that obtained through interviews and structured questionnaires, since it does not rely on recall and is required to receive remuneration for the services provided. This data source enables researchers to reconstruct "lifetime" exposure, something that would otherwise be impossible using interviews and questionnaires. It also provides exposure information that is documented independently of health outcomes. Compared to a field study, this source of exposure data is time and labour efficient, particularly when one considers the level of detail that is available. However, the use of prescription databases is not without limitations; the most important being misclassification of exposure. There are three potential sources of such misclassification in our study. First, since a "dispensed" prescription does not necessarily represent biologic exposure (i.e., may not be taken), it is possible that persons classified as "exposed" in our analysis may in fact be "unexposed" to the drug of interest. This can arise from non-compliance, treatment failure, and treatment intolerance. In all three situations, the misclassification arises from the inability

to determine the actual duration of exposure. In the context of a chronic and progressive disease, treatment failure or treatment intolerance would be most likely to lead to a switch in therapy rather than to treatment discontinuation. In our analysis this would not have lead to important exposure misclassification since our definition of "current" exposure was based on the prescription dispensed closest to the index date. A second source of exposure misclassification arises from the misspecification of the prescription duration. In our study, we assume an average duration of 35 days since duration is not available in the Saskatchewan database. It is possible that individuals classified as "past" users are in fact "current" users if their prescription duration was longer. However, our sensitivity analysis using a 60 and 90 day duration indicates that this is an unlikely source of bias. Finally, exposure misclassification can occur if individuals choose to pay out-of-pocket for medications that are either not "covered" by the drug benefit program, or have their coverage delayed. Since these prescriptions are not captured by the database, these individuals would be misclassified as "unexposed" to these medications. This is not likely to explain the increased risk we observed for users of thiazolidinediones and sulfonylureas, nor the lower risk for the "unexposed" group.

Despite careful attention to diabetes duration, progression and severity, we cannot rule out the possibility of residual confounding as we did not have information on HgA1c. On the other hand, this seems an unlikely explanation for the increased risk observed with TZDs given that the estimate remained elevated even when compared with insulin monotherapy. Moreover, the external adjustment of the sulfonylurea estimate did not appear to be affected by several unmeasured risk factors.

While the conclusions of observational studies must always be tempered by the possibility of bias, particularly confounding by indication, recent studies of the cardiovascular risks associated with the use of cyclooxygenase-2 (COX-2) inhibitors have demonstrated that carefully-designed and interpreted observational studies can have good internal validity and excellent external validity for the study of adverse outcomes.

In conclusion, the results of our study provide additional evidence of an increased risk for myocardial infarction associated with the use of TZDs, even in individuals with no history of myocardial infarction. We also observed an increased risk for users of sulfonylureas, albeit much smaller. Our findings support the need for additional studies of the safety of these agents using clinical end points,

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APPENDIX I: ETHICS APPROVAL

McGill

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April 3, 2007

Dr. Samy Suissa
Clinical Epidemiology
Royal Victoria Hospital
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Montreal, Quebec
H3A 1A1

Dear Dr. Suissa,

We are writing in response to your request for continuing review by the Institutional Review Board of the study A10-M90-03A entitled "Diabetes Mellitus and the Risk of Serious Adverse Outcomes".

The progress report was reviewed and we are pleased to inform you that re-approval for the study was provided on **April 2, 2007**, valid until **October 1, 2007.** The certification of annual review has been enclosed.

We ask that you take note of the investigator's responsibility to assure that the current protocol, study amendments and consent document are deposited on an annual basis with the Research Ethics Boards of each hospital where patient enrollment or data collection is carried out.

Should further study revision or an unanticipated development occur prior to the next review, please advise the IRB promptly.

Yours sincerely,

for Celeste Johnston, M.D.

Celeste Johnston, DEd, RN.
Co-Chair
Institutional Review Board

cc: Linda Levesque
A10-M90-03A