Building Evidence to Assess a Drug Safety Signal: the Association between Sulfonylureas and Adverse Cardiovascular Events

by

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ABSTRACT

All drugs have the potential to cause adverse events that can result in hospitalization or death. In order to protect the public health, it is critical to employ methods to detect and assess adverse drug events in a timely manner. One of the most controversial and long standing drug safety issue is the association between sulfonylureas and adverse cardiovascular events in patients with type 2 diabetes. The overall objective of this program of research was to use the cardiovascular safety signal associated with sulfonylureas as a case study to examine the application of Bradford-Hill considerations in the assessment of causal relationships. This objective was achieved through four related studies: 1) a systematic review that examined "biological plausibility" by evaluating tissue selectivity characteristics of different sulfonylureas using data from electrophysiological studies and considering the steady state concentrations of these drugs; 2) a nested case-control study that investigated "strength of association" by using provincial administrative healthcare databases to compare the effect of two commonly used sulfonylureas, gliclazide and glyburide, on risk of acute coronary syndrome; 3) a retrospective cohort study that used the same databases to evaluate the "dose-response" relationship between gliclazide and glyburide use and major adverse cardiovascular events; and 4) an observational study that relied on data from a regional ST-elevation myocardial infarction registry and examined "coherence" by extending observations from animal studies to humans with regard to the effect of sulfonylureas on infarct size.

We found that individual sulfonylureas differ with respect to tissue selectivity characteristics at usual therapeutic doses, with some sulfonylureas being more selective to pancreatic receptors; while, other sulfonylureas bind non-selectively to pancreatic and cardiac receptors. These observations imply that individual sulfonylureas might differ in their ability to abolish ischemic conditioning, a protective mechanism to protect myocardium at time of acute ischemia. To confirm these findings, we found in the nested case-control study that patients using glyburide, a sulfonylurea that binds non-selectively

to cardiac and pancreatic receptors, had a small but significantly higher risk of acute coronary syndrome events than patients using gliclazide, a sulfonylurea that is more selective to pancreatic receptors. We also found that patients using higher doses of glyburide had a higher risk of major adverse cardiovascular events compared to patients using lower doses of the drug. In contrast, we did not observe a dose-related difference in cardiovascular risk for gliclazide users. Finally, we demonstrated that sulfonylurea users had a larger infarct size compared to non-sulfonylurea users. However, there was no difference on infarct size between glyburide and gliclazide users, likely due to lack of adequate power in our study.

These findings add further evidence that there are important differences among sulfonylureas, with gliclazide appearing to be associated with a lower risk of adverse cardiovascular events compared to glyburide. Clinicians should consider these differences when initiating sulfonylureas in type 2 diabetes patients. Further, we approached this assessment of the cardiovascular safety of sulfonylureas by evaluating elements of the Bradford-Hill considerations for casual relationships. We provided a case study on using these elements to assess causality in pharmacoepidemiology studies.

PREFACE

This thesis is an original work by Mr. Ahmed S. Abdelmoneim. The research projects, of which this thesis is a part, received research ethics approval from the Health Research Ethics Board (HREB) at the University of Alberta.

- "Is there a difference in cardiovascular risk amongst the sulfonylureas?", No: Pro00009813, October 9, 2009.
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DEDICATION

To my incredibly loving wife…

To my endlessly supportive family…

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Chapters 3 and 4 were based in part on de-identified data provided by Alberta Health. The interpretation and conclusions contained herein are those of the researchers and do not necessarily represent the views of the Government of Alberta. Neither the Government of Alberta nor Alberta Health expresses any opinion in relation to this study.

Chapter 5 was based in part on data provided by Alberta Health Services and Covenant Health. The interpretation and conclusions contained herein are those of the researchers and do not necessarily represent the views of the data providers.

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ABBREVIATIONS

ABC	Alberta Blue Cross
ACS	acute coronary syndrome
ADE	adverse drug event
BMI	body mass index
CI	confidence interval
CK-MB	creatine kinase-myocardial band
COX-II	cyclooxygenase-2
C_{ss}	steady state concentration
DDD	defined daily dose
DNA	deoxyribonucleic acid
FDA	Food and Drug Administration
HbA_{1c}	hemoglobin A_{1c}
HR	hazard ratio
IC_{50}	half-maximal inhibitory concentration
ICD	International Classification of Diseases
K_{ATP}	ATP-sensitive potassium
MACE	major adverse cardiovascular event
Max ck	maximum recorded total creatine kinase
Max cTnI	maximum recorded troponin I
MRI	magnetic resonance imaging
NNH	number needed to harm
OR	odds ratio
PY	person-years
RCT	randomized controlled trial
RR	relative risk
SD	standard deviation
SPECT	single-photon emission computed tomography
STEMI	ST-elevation myocardial infarction
SUR	sulfonylurea receptor
TZDs	thiazolidinediones
US	Unites States
VHR	Vital Heart Response
VIF	variance inflation factor
WHO	World Health Organization

TRIAL ACRONYMS

ACCORD	Action to Control Cardiovascular Risk in Diabetes
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation
CAROLINA	CARdiovascular Outcome Trial of LINAgliptin Versus Glimepiride in Type 2 Diabetes
ELIXA	Evaluation of LIXisenatide in Acute Coronary Syndrome
TECOS	Trial Evaluating Cardiovascular Outcomes with Sitagliptin
TOSCA.IT	Thiazolidinediones Or Sulphonylureas and Cardiovascular Accidents. Intervention Trial
UGDP	University Group Diabetes Program
UKPDS	United Kingdom Prospective Diabetes Study
VADT	Veterans Affairs Diabetes Trial

CHAPTER 1

Introduction

1.1. Statement of the Problem

1.1.1. Assessment of a Drug Safety Signal

No drug is free from risk, and the consequences of adverse drug events (ADEs) represent a major patient safety and public health challenge.[1] In the United States (US), it has been estimated that fatal ADEs was between the fourth and sixth leading cause of death, not far behind cancer and cardiovascular disease.[2] While in Canada, ADEs account for approximately 23,750 deaths and 185,000 hospital admissions each year.[3] The economic burden of ADEs on our healthcare system is substantial, costing an estimated $177.4 billion annually.[4,5] Although the impact of ADEs is very concerning, it is important to note that almost 70% of ADEs resulting in hospitalizations are avoidable.[6,7] From a regulatory perspective, organizations like the Food and Drug Administration (FDA) and Health Canada can recommend label revision, restrict access or withdraw drugs from the market because of ADEs and other safety concerns. Indeed, between 1997 and 2011, Health Canada has withdrew 25 drugs from the Canadian market for safety reasons.[8]

The mission of national drug regulatory authorities is to provide the public with safe, high-quality, therapeutically effective drugs.[9–11] After passing rigorous criteria involving preclinical testing and 3 phases of clinical studies, a drug is approved for marketing when its benefits are judged to outweigh its risks. Although premarketing randomized controlled trials (RCTs) are the gold standard for evaluating drug efficacy, these sources of evidence have important limitations when it comes to assessing safety.[12] Premarketing clinical trials often use stringent inclusion and exclusion criteria, have a limited sample size, and have short-term follow-up. Moreover, the chance of detecting an ADE during

premarketing clinical trials is even more unlikely if the adverse event is rare, has a long induction period, or is unique to high-risk populations. Once on the market, it is even more difficult to predict the type and frequency of adverse events that might arise as drugs are used by a diverse population (age, gender, race, concomitant drugs, disease severity, and comorbidities) and can be used under different conditions, with different doses, duration of use, and different indications (off-label).[13,14]

Realizing limitations of the current regulatory drug approval process, initiatives have been developed to improve assessment of a drug's safety, quality and effectiveness.[15–19] New drug safety regulations recommend focusing on post-marketing drug monitoring and evaluation as a vital tool to identify safety signals arising from the use of drugs by the general population.[17,18,20] According to the World Health Organization (WHO), a safety signal is "reported information on possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously".[21] Traditionally, detection of safety signals was achieved through spontaneous reporting of adverse events associated with drug by clinicians and healthcare agencies.[13] New initiatives and regulations are rapidly evolving to aid in the process of safety signal detection, such as active surveillance and post-marketing safety study requirements.[22,23]

However, detecting a safety signal does not establish a causal link between the drug and a suspected adverse event. In fact, further testing and assessment is necessary to confirm an adverse event is caused by the drug.[24–26] While RCTs are considered the most rigorous approach in determining a causal link between a drug and an outcome, this source is often impractical or unethical for examining a drug safety signal.[12] As such, national drug regulatory authorities recommend the use of non-randomized observational methods, such as registries and surveys to complement RCTs in the assessment of safety singals.[27] With the development of powerful computers and large administrative healthcare databases, the use of pharmacoepidemiology studies has emerged as a powerful tool to assess drug safety signals in real-world settings.[28,29] These databases collect demographic information as well as detailed clinical information on patients' diagnoses, diagnostic test results, hospital admissions

and prescriptions filled and therefore present a great opportunity to study drugs with a wealth of data on real-world use. Being routine byproducts of the healthcare delivery system, these databases also offer the advantage of accessing information with efficiency in terms of time, manpower, and costs.[30]

To guide the process of assessing causal relationships in pharmacoepidemiology studies, many investigators follow a framework proposed by Sir Austin Bradford Hill in 1965.[31–33] The Bradford-Hill considerations are: biological plausibility, temporality, strength of association, coherence, dose-response relationship, consistency, specificity and analogy. Assessment of each consideration provides useful information on the relationship between a drug and a suspected adverse event; however, each element is neither necessary nor sufficient to confirm causality.[32] Several previous studies have used the Bradford-Hill considerations to assess causal relationships in drug safety signals as in the cases of cisparide–induced QT prolongation, flupirtine-induced liver injury and oral contraceptive-induced venous thromoembolism.[34–36] It is noteworthy, however, there is no predetermined algorithm or formula to judge causality when these elements are applied to any suspected causal relationship.

In this program of research, we used the Bradford-Hill considerations to assess a longstanding safety signal associated with the use of sulfonylureas in type 2 diabetes patients. In the next section, we focus on historical aspects and current evidence to support or refute this safety signal.

1.1.2. A Drug Safety Signal Example: Sulfonylureas and Adverse Cardiovascular Events

Diabetes epidemiology and cardiovascular complications

Diabetes mellitus is at epidemic proportions worldwide. The International Diabetes Federation estimates more than 387 million people are affected by diabetes globally, and projects this figure to rise to 592 million (or approximately 10% of the world population) by 2035.[37] In Canada, there are 2.7 million (7.6%) people living with diabetes and this prevalence is projected to increase to 4.2 million (10.8%) by 2020.[38] Almost 90% of people with diabetes have type 2 diabetes.

Type 2 diabetes is a major risk factor for cardiovascular disease. The risk of developing a cardiovascular disease is 2- to 3-fold higher in people with type 2 diabetes than those without diabetes.[39] This higher risk is likely due to a clustering of cardiovascular risk factors in people with diabetes.[40–42] In a landmark trial, patients with type 2 diabetes and no previous myocardial infarction had a similar risk of coronary heart disease compared to patients without type 2 diabetes and a previous myocardial infarction.[43] Additionally, cardiovascular disease is the primary cause of mortality in people with type 2 diabetes, accounting for approximately one half of all deaths among people with type 2 diabetes.[44]

Cardiovascular safety of antidiabetic drugs

In addition to the cardiovascular risk conferred by diabetes itself, some drugs used to manage diabetes appear to increase the risk of adverse cardiovascular events. Perhaps the most well-known example is the association between thiazolidinediones (TZDs), especially rosiglitazone, and an increased risk of myocardial infarction, stroke, heart failure, and all-cause mortality.[45–47] These safety concerns prompted the FDA to require clinical trial evidence attesting to the cardiovascular safety of all new antidiabetic drugs.[48]

Like TZDs, sulfonylureas were linked to adverse cardiovascular events. This cardiovascular safety signal of sulfonylureas was first raised in 1970s.[49] More than forty years later there is no consensus on the safety of this widely used class of antidiabetic drug.[50] With the cardiovascular safety of newer antidiabetic agents still under study, it is important to find the true association between sulfonylureas and risk of adverse cardiovascular events.[51]

Cardiovascular safety of sulfonylureas

Sulfonylureas have been a cornerstone in the management of people with type 2 diabetes for over 60 years.[52] Despite the well-recognized limitations of hypoglycemia, weight gain, and secondary failure associated with sulfonylurea use,[53] clinical practice guidelines recommend sulfonylureas as second-line therapy when metformin fails, and even as first-line therapy under certain circumstances.[54,55] Indeed, many studies examining the patterns of antidiabetic drug use have identified that sulfonylureas are commonly used for people with

type 2 diabetes, although their use has been declining in recent years.[56–59] Perhaps the popularity of sulfonylureas is based on familiarity, reliable efficacy to reduce glycaemia, and availability at low cost.

For many years, however, the use of sulfonylureas in people with type 2 diabetes and their relationship with adverse cardiovascular events has been questioned.[60,61] These safety questions were first raised following publication of the UGDP trial results in 1970.[49] The UGDP was a 823-person, multi-center, randomized, placebo-controlled, clinical trial designed to compare the efficacy of tolbutamide, insulin, and diet alone. However, because of an excess of cardiac deaths in people treated with the sulfonylurea drug, tolbutamide (26 [12.7%] of 204) compared to placebo (10 [4.9%] of 205) ($p<0.01$), investigators decided to terminate this arm of the study early.[49] There has been much criticism regarding the results of the UGDP, mainly due to its methodological flaws with the inclusion of participants without diabetes, poor randomization, and inadequate verification of cardiovascular deaths.[62] Nevertheless, findings of the UGDP led the FDA to require a black-box warning on all sulfonylurea packaging indicating a possible cardiovascular risk associated with sulfonylureas.[63]

Twenty-eight years later, findings from a much larger study, the UKPDS, countered those of the UGDP.[64] The UKPDS followed 3,867 newly diagnosed people with type 2 diabetes; while randomly assigning them to intensive treatment with a sulfonylurea (glyburide [glibenclamide], glipizide, or chlorpropamide) or insulin, or conventional treatment with diet alone. After a median follow-up of 10 years, intensive glycemic control was associated with reduced morbidity and mortality compared to conventional therapy. There was no evidence that sulfonylureas were associated with increased mortality (Relative Risk [RR] 0.91; 95% CI 0.73 – 1.15 and RR 1.02; 95% confidence interval [CI] 0.82 – 1.27 for glyburide and chlorpropamide; respectively).[64]

To resolve this apparent conflict between the UGDP and UKPDS trial results, a remarkable number of studies have looked at the association between sulfonylureas and adverse cardiovascular events. However, the majority of evidence is not generated from experimental trials that randomly allocated people to a sulfonylurea or control, which makes it difficult to firmly establish causality. In addition, findings from observational studies are somewhat

conflicting, with some studies suggested a higher risk of adverse cardiovascular events associated with sulfonylurea use,[65–68] others suggesting a lower risk,[69] and others finding no difference in risk.[70–72]

In an effort to pool data from all available studies, nine different meta-analyses have been carried out, with 7 published in the last few years.[73–81] Table 1-1 provides a summary of all published meta-analyses evaluating the cardiovascular safety of sulfonylureas. Collectively, data from observational studies suggest an association between sulfonylurea use and adverse cardiovascular events. However, considering the biased nature of observational studies, meta-analyses based on this type of study should also be considered weak sources of evidence. Evidence from RCTs; in contrast, is less consistent, with the majority of evidence from this type of study suggesting a neutral effect as opposed to a harmful effect of sulfonylureas. It is important to note that the quality of these meta-analyses is as good as the studies they are based on.

Limitations of the current literature on sulfonylureas

Part of the reason that we still have not reached consensus on the cardiovascular safety of sulfonylureas is because the current literature has important limitations. Although appropriately designed RCTs are at the top of the evidence hierarchy when assessing causality,[12] current evidence from clinical trials on the cardiovascular safety of sulfonylureas is limited for several reasons.

First, although the overall number of clinical trials reporting cardiovascular events with sulfonylureas is quite substantial, the vast majority were not designed to assess the effect of these drugs on this outcome. These studies were generally designed to examine the effect of sulfonylureas on short-term outcomes, like blood glucose response or risk of hypoglycemia and therefore were limited by small sample size and short duration of follow up. Perhaps more importantly, adverse cardiovascular events were not always reported or adjudicated.[78] In fact, since the publication of the UGDP trial, only one long-term clinical trial has been specifically designed to assess cardiovascular events in people randomized to a sulfonylurea or control.[82] In this relatively small trial from China, 304 patients with type 2 diabetes and a history of coronary artery disease

were randomized to receive either glipizide or metformin and were followed for a median of 5 years. Treatment with metformin was associated with a substantially lower risk of major cardiovascular events compared with glipizide (Hazard Ratio [HR] 0.54; 95% CI 0.30–0.90).[82] Despite this finding, the study was criticized for several reasons, including failing to adequately balance baseline characteristics between the study groups and the lack of a washout period before starting the study drugs.[83] Future trials in the area, like the TOSCA.IT and the CAROLINA trials, will be sufficiently powered to measure cardiovascular events, but results are not expected for several years.[84,85]

Second, major diabetes trials that followed the UGDP, i.e. ACCORD, ADVANCE and VADT, have focused on evaluating the effect of glycemic control rather than investigating the effects of a specific antidiabetic drug.[86–88] Unfortunately, information from these trials has limited utility for teasing out the effect of a specific antidiabetic drug on cardiovascular events. Any observed association between a specific drug and adverse cardiovascular events may be confounded by the level of glycemic control.

Third, some investigators have suggested that the apparent increased risk of adverse cardiovascular events observed with sulfonylureas might actually be in contrast to a cardioprotective effect of metformin.[89] Despite this perceived benefit with metformin, other investigators have argued against a protective effect of metformin on cardiovascular complications.[90]

In contrast to RCTs, there are numerous observational studies specifically designed to evaluate cardiovascular events associated with sulfonylureas in people with type 2 diabetes (Appendix A). Nonetheless, findings from observational studies are often seen as hypothesis-generating rather than a strong source of causal evidence due to several critcisms.[91] First, residual confounding is evident in most of these studies due lack of information on important cardiovascular risk factors like blood pressure, renal function, body mass index (BMI), smoking status, and hemoglobin A_{1c} (HbA_{1c}).[92,93] Complex analytic techniques like high dimensional propensity score matching and instrumental variable adjustment, have been used but they are unlikely to control for all unmeasured confounding variables.[94,95] Second, selection bias can arise in these studies when prescribing of drugs is based on indication or disease

severity.[96,97] For example, metformin monotherapy was often used as the main comparator in observational studies of sulfonylureas.[98–100] However, this approach could be biased in favor of metformin because people using this drug are inherently different (i.e. they may be younger, have less severe hyperglycemia, have a shorter duration of diabetes, or have fewer comorbidities as clinical practice guidelines recommend using metformin as first-line therapy) compared to those using a sulfonylurea.[54–56]

Is there a causal link?

Given inconsistences in findings from clinical trials and observational studies and limitations in current literature, Bradford-Hill considerations could provide some insight into the possible causal relationship between sulfonylureas and adverse cardiovascular events as follows:

Biological plausibility. Among the suggested plausible mechanisms, two are commonly used to explain the adverse cardiovascular effects of sulfonylureas. In the first, sulfonylurea-induced hypoglycemia has been suspected as the trigger for harmful cardiovascular effects. Acute hypoglycemia might provoke a sympathetic response that could precipitate transient cardiac stress leading to increased myocardial oxygen consumption, myocardial ischemia, QT prolongation and arrhythmia.[101–105] In the second mechanism, sulfonylureas are thought to abolish the protective effect of ischemic conditioning, a protective response triggered by brief episodes of ischemia and reperfusion to limit damage following myocardial infarction.[60,106–108] Additional plausible mechanisms include accumulation of visceral fat and increased plasma proinsulin: insulin ratio.[76]

When considering the plausible biologic mechanisms, there may be important differences in pharmacodynamic, pharmacokinetic, and pharmacologic properties among sulfonylureas. For example, the risk of hypoglycemia varies among sulfonylureas and is highest with glyburide.[109,110] Sulfonylureas also appear to vary in time to maximum blood concentration (from 1-3 hours for glipizide to 4-6 hours for gliclazide), half-life (from 5 hours for glimepiride to 6-12 hours for gliclazide), metabolism (glyburide has active metabolites, while gliclazide and glipizide have inactive metabolites), and elimination (from 50% renal elimination of glyburide to 80% renal elimination of glipizide).[52,111–118]

Additionally, it seems that individual sulfonylureas could have different abilities to abolish ischemic conditioning.[108,119] Therefore, the potential cardiovascular effects could be an individual drug effect rather than a class effect. Most of the previous observational studies, however, did not consider these potential differences between individual sulfonylureas.[50]

Temporality. There is some evidence of this consideration in observational studies, especially when studying mortality because drug exposure precedes the outcome.[65,120] More importantly, according to the ischemic conditioning theory, sulfonylureas need to be at the site of action at the time of ischemic conditioning to interfere with it.[107,121] Previous observational studies have not considered this because exposure was often based on sulfonylurea use at the start of an observation period rather than identifying exposure within the days preceding the cardiovascular event.[122–124]

Strength of association. Point estimates observed from pooled observations in meta-analyses reveal a rather weak association between sulfonylurea use and adverse cardiovascular events (pooled point estimates 0.53 – 2.72).[74,76]

Coherence. Administration of sulfonylureas in animal models showed harmful cardiac effects.[125–132] Similar effects in humans have not been fully examined.[133,134]

Dose-response. There is scarce data to support a dose-response relationship between sulfonylureas and adverse cardiovascular events in humans.[135,136]

Consistency. There is inconsistency of findings from RCTs and observational studies on this topic.

Experimentation. Current evidence from RCTs on the cardiovascular safety of sulfonylureas is limited. However, current ongoing trials might provide some evidence.[84,85]

Specificity. Since cardiovascular disease is a multifactorial condition, specificity is not met in this case.

Analogy. As other antidiabetic drugs, like the TZDs, are suspected of causing adverse cardiovascular events, so can sulfonylureas.

To conclude, most elements from the Bradford-Hill considerations for causal relationships are not fulfilled. Thus, a causal relation cannot be inferred from the current literature. It is therefore of utmost importance that future studies generate new evidence on the relation between sulfonylureas and adverse cardiovascular events.

1.2. Summary

Adverse drug events are common, significant, costly, and can be fatal. Prior to approval for marketing, safety information is often limited to data reported in premarketing RCTs conducted in carefully selected individuals. Post-marketing drug monitoring and evaluation is vital to identify safety signals arising from the use of drugs by the general population. Although RCTs are considered the most rigorous approach to assess causal relationships, this source is often impractical or unethical for examining safety questions. Thus, the use non-randomization methods, such as pharmacoepidemiology studies, guided by Bradford-Hill considerations, could be a useful framework for evaluating the possible adverse effects of a drug.

As type 2 diabetes mellitus is reaching new epidemic proportions around the world, more people are expected to suffer from cardiovascular complications. In recent years, the cardiovascular safety of antidiabetic drugs has been a major topic of discussion especially in the light of restricting access to rosiglitazone and new regulatory requirements to evaluate safety of new antidiabetic drugs. For many years, the cardiovascular safety signal associated with sulfonylureas has been under contentious debate. Although several hypotheses linking sulfonylureas to adverse cardiovascular events exist, none provide conclusive evidence. Adding to the controversy, current clinical trials and observational studies provide inconsistent, and sometimes conflicting, evidence for the cardiovascular effects of sulfonylureas. This program of research focused on using Bradford-Hill considerations as a framework to assess the association between sulfonylurea use and adverse cardiovascular events. In the light of this, we investigated some of the Bradford-Hill elements that were not addressed in the current literature.

1.3. Objectives

The overall objective of this program of research was to use the cardiovascular safety signal associated with sulfonylurea use as a case study to examine the application of Bradford-Hill considerations in the assessment of a causal relationship. To achieve this, we had several sub-objectives. First, to examine the biological mechanism by investigating whether or not there was a difference in tissue selectivity characteristics among individual sulfonylureas. Second, to investigate whether there were differences between individual sulfonylureas on adverse cardiovascular events. Third, to assess the dose-response relationship between sulfonylureas and adverse cardiovascular events. Finally, to extend our understanding of a possible biological mechanism and determine if there is coherence between animal models and clinical events in humans by examining the effect of sulfonylureas on myocardial infarct size.

1.4. Program of Research

A series of four studies contributed to the overall study objectives. The first study (Chapter 2) was a systematic review to evaluate the tissue selectivity characteristics of different sulfonylureas using data from electrophysiological studies and considering the steady state concentrations of these drugs. The second and third studies (Chapters 3 and 4) were observational studies that used data from Alberta Health. A nested case-control study (Chapter 3) compared the effect of gliclazide and glyburide exposure on risk of acute coronary syndrome. The dose-response relationship (Chapter 4) between gliclazide and glyburide and adverse cardiovascular events was examined in a retrospective cohort analysis. The last study (Chapter 5) used data from a regional ST-elevation myocardial infarction (STEMI) registry to evaluate the impact of sulfonylurea use on infarct size in a group of type 2 diabetes patients.

Table 1-1. Published meta-analyses of clinical trials and observational studies of sulfonylureas and cardiovascular events

Meta-analysis	*Type of studies included (n)*	*Sulfonylurea vs. comparator*	*Outcome*	*Pooled point estimates*
Simpson, 2015[73]	RCT (7), observational (17)	Gliclazide[(a)], Glimepiride[(b)], Glipizide[(c)], Tolbutamide[(d)], Chlorpropamide[(e)] vs. glyburide	All mortality	[(a)]0.65 (0·53–0·79) [(b)]0·83 (0·68–1·00) [(c)]0·98 (0·80–1·19) [(d)]1·13 (0·90–1·42) [(e)]1·34 (0·98–1·86)
Zhang, 2014[74]	RCT (4)	DDP-IV inhibitors vs. SU	CV events	0.53 (0.32 – 0.87)
Landman, 2014[75]	RCT (9)	Gliclazide vs. OAD	CV events	0.95 (0.57 – 1.61)
	RCT (15)	Gliclazide vs. OAD	CV mortality	0.81 (0.26 – 2.47)
	RCT (17)	Gliclazide vs. OAD	All mortality	1.50 (0.62 – 3.62)
Forst, 2013[76]	Observational (4)	SU vs. non SU	CV mortality	2.72 (1.95 – 3.79)
	Observational (12)	SU vs. non SU	All mortality	1.92 (1.48 – 2.49)
Phung, 2013[77]	Observational (9)	SU vs. no SU	CV mortality	1.26 (1.18 – 1.34)
	RCT (7)	SU vs. no SU	CV mortality	1.22 (0.63 – 2.39)
Monami, 2013[78]	RCT (30)	SU vs. placebo and/or AD	MACE	1.08 (0.86 – 1.36)
	RCT (37)	SU vs. placebo and/or AD	All mortality	1.22 (1.01 – 1.49)
Hemmingsen,* 2013[79]	RCT (3)	SU monotherapy vs. MET mono	CV morbidity	0.67 (0.48 – 0.93)
	RCT (6)	SU monotherapy vs. MET mono	CV mortality	1.47 (0.54 – 4.01)
	RCT (6)	SU monotherapy vs. MET mono	All mortality	0.98 (0.61 – 1.58)
Rao, 2008[81]	Observational (5)	SU + MET vs. diet, MET mono, SU mono	CV mortality or hospitalization	1.43 (1.10 – 1.85)
	Observational (4)	SU + MET vs. diet, MET mono, SU mono	CV mortality	1.29 (0.73 – 2.27)
	Observational (7)	SU + MET vs. diet, MET mono, SU mono	All mortality	1.19 (0.88 – 1.62)
Selvin, 2008[80]	RCT (5)	SU vs. Placebo or any AD	CV morbidity	0.89 (0.71 – 1.11)
	RCT (5)	SU vs. Placebo or any AD	CV mortality	0.92 (0.68 – 1.26)
	RCT (6)	SU vs. Placebo or any AD	All mortality	0.90 (0.70-1.15)

* Only results comparing second generation sulfonylureas against metformin are shown here.
AD: antidiabetic drug; CV: cardiovascular; DDP-IV: Dipeptidyl peptidase-IV; MACE: major adverse cardiovascular event; MET: metformin; mono: monotherapy; RCT: randomized controlled trial; SU: sulfonylurea; OAD: oral antidiabetic drug

CHAPTER 2

Variations in Tissue Selectivity amongst Insulin Secretagogues: A Systematic Review[1]

2.1. Abstract

Background

Insulin secretagogues promote insulin release by binding to sulfonylurea receptors on pancreatic β-cells (SUR1). However, these drugs also bind to receptor isoforms on cardiac myocytes (SUR2A) and vascular smooth muscle (SUR2B). Binding to SUR2A/SUR2B may inhibit ischemic conditioning, an endogenous protective mechanism enabling cardiac tissue to survive periods of ischemia. This study was designed to identify insulin secretagogues that selectively bind to SUR1 when given at therapeutic doses.

Methods

Using accepted systematic review methods, three electronic databases were searched from inception to June 13, 2011. Original studies measuring the half-maximal inhibitory concentration (IC_{50}) for an insulin secretagogue on ATP-sensitive potassium (K_{ATP}) channels using standard electrophysiological techniques were included. Steady state concentrations (C_{SS}) were estimated from the usual oral dose and clearance values for each drug.

Results

Data were extracted from 27 studies meeting all inclusion criteria. IC_{50} values for SUR1 were below those for SUR2A/SUR2B for all insulin secretagogues and

[1] A version of this chapter has been published as *Abdelmoneim S, Hasenbank SE, Seubert JM, Brocks DR, Light PE, Simpson SH. Variations in tissue selectivity amongst insulin secretagogues: a systematic review. Diabetes Obes Metab. 2012 Feb;14(2):130–8.* Permission to reuse this copyrighted material was provided by the publisher, John Wiley and Sons, License Number 3678870751558.

addition of C_{SS} values identified three distinct patterns. The C_{SS} for gliclazide, glipizide, mitiglinide and nateglinide lay between IC_{50} values for SUR1 and SUR2A/SUR2B, suggesting these drugs bind selectively to pancreatic receptors. The C_{SS} for glimepiride and glyburide was above IC_{50} values for all 3 isoforms, suggesting these drugs are non-selective. Tolbutamide and repaglinide may have partial pancreatic receptor selectivity because IC_{50} values for SUR1 and SUR2A/SUR2B overlapped somewhat, with the C_{SS} in the midst of these values.

Conclusion

Insulin secretagogues display different tissue selectivity characteristics at therapeutic doses. This may translate into different levels of cardiovascular risk.

2.2. Introduction

Sulfonylureas are a class of oral antidiabetic drugs used to control blood glucose in patients with type 2 diabetes. Although considered second-line agents in Canada and the United States,[54,55] sulfonylureas are the most common alternative when metformin monotherapy fails or is contraindicated.[56,137] Sulfonylureas and a related class of drugs, the glinides, are generally referred to as insulin secretagogues. These drugs promote insulin release from pancreatic β-cells by binding to sulfonylurea receptors and inhibiting K_{ATP} channels. Inhibition of K_{ATP} channels results in membrane depolarization and calcium influx through voltage-gated calcium channels. These events lead to an increase in intracellular calcium and subsequent exocytosis of insulin-containing granules.[138]

In addition to pancreatic β-cells, K_{ATP} channels are also located in other excitable cell types such as cardiac myocytes, vascular smooth muscle, skeletal muscle, and neurons.[119] K_{ATP} channel activation in cardiac myocytes results in shortening of the action potential and reduction of cardiac workload, while K_{ATP} channel activation in vascular smooth muscle promotes muscle relaxation and vasodilatation.[139,140] Both actions are believed to contribute to ischemic conditioning, an endogenous protective mechanism in which brief episodes of ischemia and reperfusion (as seen during angina episodes) can enable cardiac tissue to be more resilient during a more profound ischemic insult that results in myocardial infarction.[106,107,141] Although insulin secretagogue-mediated inhibition of pancreatic K_{ATP} channels produces the desired therapeutic effect, additional inhibition of K_{ATP} channels with different molecular conformations in cardiac myocytes and vascular smooth muscle may contribute to adverse cardiovascular effects. Insulin secretagogue-mediated inhibition of cardiovascular K_{ATP} channels may reduce beneficial vasorelaxation, impede ischemic conditioning and promote ischemic damage.[132,142] Indeed, observational studies have suggested that insulin secretagogue use is associated with an increased risk of cardiovascular events in patients with type 2 diabetes.[66,69–72,134,143–148]

K_{ATP} channels are hetero-octamers of four inwardly rectifying pore-forming potassium channel subunits (Kir6.1 or Kir6.2 encoded by the KCNJ8 and KCNJ11 genes respectively) and four SUR subunits (Figure 2-1A). There are

two isoforms of SUR: SUR1 and SUR2 encoded by the ABCC8 and ABCC9 genes respectively. Alternative splicing of the ABCC9 gene yields two SUR2 splice variants, SUR2A and SUR2B, that differ only in the distal C-terminal of the protein (Figure 2-1B). Distinct isoforms and splice variants of the SUR subunit are expressed in different tissues and confer many of the pharmacological properties to the K_{ATP} channel hetero-octamer. The dominant subunits expressed in endocrine cell types, such as pancreatic β-cells in humans, are Kir6.2 and SUR1. Whereas the sarcolemmal membrane of cardiac myocytes and skeletal muscle express the Kir6.2 and SUR2A subunits and vascular smooth muscle predominately expresses Kir6.1and SUR2B.[149]

Sulfonylurea and glinide drugs can be classified according to their K_{ATP} channel binding site as A-site, B-site, or AB-site drugs (Figure 2-1C). The A-site is contained within the cytosolic loops linking trans-membrane segments 14-16 of the SUR subunit. The B-site resides in the linker between the trans-membrane segments 5-6 of the SUR subunit and the N-terminus of the Kir6.2 subunit (Figure 2-1B).

In general, insulin secretagogues have a higher binding affinity for SUR1 in the pancreas relative to SUR2A and SUR2B in the heart. While the difference between SUR1 and SUR2A/SUR2B affinities may be quite profound for some drugs (16,000 fold difference for gliclazide), others, like glimepiride, have very similar affinities for all 3 isoforms.[150,151] These differences in K_{ATP} channel binding affinities could be exploited if the steady state concentration achieved with usual therapeutic doses falls between the binding affinities for SUR1 and SUR2A/SUR2B. Insulin secretagogues with these characteristics would selectively bind to pancreatic receptors when given at usual therapeutic doses and possibly have a lower risk of cardiovascular events, which could have important clinical implications.[151–153]

With these issues in mind, the objectives for this systematic review were twofold. First, summarize the literature reporting SUR1, SUR2A, and SUR2B binding affinities for clinically available insulin secretagogues. Second, estimate the steady-state concentration of these drugs at usual therapeutic doses and compare it to the binding affinities at each receptor. We hypothesized that these

combined sources of information would identify drugs that selectively act on the pancreas when given at usual therapeutic doses.

2.3. Methods

With assistance from a medical research librarian, we searched PubMed, EMBASE, and the Web of Science from the database inception date to June 13, 2011. Database-specific search terms for sulfonylurea, binding affinity, K_{ATP} channel, SUR1, SUR2A, and SUR2B were used to identify citations. The full search strategy is attached to Appendix B. The electronic database search was supplemented by hand-searching reference lists of review articles describing insulin secretagogue activity on K_{ATP} channels and included studies. No language restrictions were imposed.

Once the searches were combined and duplicates removed, two investigators independently screened titles and abstracts to identify potentially relevant citations. We excluded citations that did not report original study data or investigate an insulin secretagogue. The full article of each potentially relevant citation was reviewed to determine if it met the following inclusion criteria: 1) original experimental study, 2) wild-type cells or unaltered SUR and K_{ATP} channel proteins were used, 3) the cell line, SUR isoform, and electrophysiology technique were specified, 4) the experimental environment approximated normal physiologic parameters, and 5) the study reported a concentration required to produce half-maximal inhibition of K_{ATP} channel electrical activity (IC_{50}). Disagreements regarding inclusion were resolved by consensus.

Data extraction was performed by one investigator using a standardized data collection form and a second investigator verified completeness and accuracy. We recorded the cell line used, sources for the SUR and K_{ATP} channel proteins, electrophysiological technique performed, insulin secretagogue investigated, and IC_{50} values.

Plasma C_{SS} for usual therapeutic doses were estimated using the defined daily dose (DDD) established by the World Health Organization (WHO) and oral clearance values for each drug.[154] Clearance data in plasma were obtained from

pharmacokinetic studies in healthy volunteers.[97,155–161] The following equation was used to calculate a C_{SS}:

$$C_{SS} = DDD / (Cl/F)$$

C_{SS}: steady-state plasma concentration, DDD: defined daily dose, Cl/F: oral clearance

The IC_{50} and C_{SS} values for each insulin secretagogue were plotted on a semi-log graph and inspected visually to identify patterns of SUR affinities.

2.4. Results

A total of 2,087 unique citations were identified, of which 100 were considered potentially relevant (Figure 2-2). After reviewing the full articles, investigators disagreed on the allocation of 11 and following discussion, determined that 27 studies met all inclusion criteria.[162–188] IC_{50} data for 14 insulin secretagogues were abstracted, of which six (HMR 1098, HMR 1883, LY397364, LY389382, midaglizole, meglitinide) are investigational drugs or not clinically available. The remaining eight insulin secretagogues are available for clinical use.

All included studies calculated the IC_{50} value using similar methods. Dose-response curves were created by measuring trans-membrane K_{ATP} channel currents at 5-7 different drug concentrations. The amount of K_{ATP} channel current at each concentration was expressed as a fraction of the conductance measured in a control solution without any drug. The IC_{50} value was derived from a standard formula and reflects the drug concentration that would inhibit 50% of K_{ATP} channel current when measured in a drug-free solution.

The included studies used a variety of cell lines and sources for SUR and K_{ATP} channel proteins to obtain the IC_{50} values (Table 2-1). The most common expression systems were Xenopus Laevis oocyte (XLO), and human embryonic kidney (HEK) 293T cells. The most common sources for SUR and K_{ATP} channel proteins were Deoxyribonucleic acid (DNA) sequences isolated from rats and mice. Most studies used either a whole cell or inside-out patch clamp technique to measure K_{ATP} channel currents.

Despite differences in experimental designs, there were consistent observations across the in vitro studies. All insulin secretagogues had a higher

affinity for SUR1 relative to SUR2A/SUR2B because lower concentrations were required to achieve IC_{50} (Figure 2-1). Plotting IC_{50} and C_{SS} values for the eight insulin secretagogues identified three distinct patterns. The first pattern includes insulin secretagogues that appear to bind selectively to pancreatic tissue (SUR1) when given at usual therapeutic doses. Glipizide, gliclazide, mitiglinide, and nateglinide had a clear separation between all reported IC_{50} values for SUR1 and SUR2A/SUR2B. The differences in tissue-specific affinities were further highlighted when plasma C_{SS} values for these drugs were found to lie between the IC_{50} ranges for SUR1 and SUR2A/SUR2B. The second pattern includes insulin secretagogues that may have partial selectivity for pancreatic receptors when given at usual therapeutic doses. Although there is a clear separation between reported IC_{50} values for SUR1 and SUR2A/SUR2B, the plasma C_{SS} for tolbutamide was in the midst of reported values for SUR2A. In contrast, for repaglinide, the ranges of reported IC_{50} values for SUR1 overlapped with those for SUR2A/SUR2B, while the plasma C_{SS} was in the midst of these values. The third pattern includes insulin secretagogues that appear to have no tissue selectivity at usual therapeutic doses. Although reported IC_{50} values for SUR1 overlapped with those for SUR2A/SUR2B, the plasma C_{SS} for glimepiride and glyburide were above these values.

2.5. Discussion

This review demonstrates that insulin secretagogues have a range of affinities for K_{ATP} channels with different SUR isoform composition, resulting in different abilities to inhibit K_{ATP} channel activity. When the plasma C_{SS} of a usual therapeutic dose is also considered, the range of SUR isoform affinities may be exploited. Some insulin secretagogues appear to selectively bind to pancreatic receptors. The C_{SS} of gliclazide, glipizide, mitiglinide and nateglinide exceeds the levels required to inhibit pancreatic K_{ATP} channels, but does not reach the levels required to significantly inhibit cardiac myocyte or vascular smooth muscle K_{ATP} channels. Whereas glyburide and glimepiride may be non-selective because the C_{SS} for these drugs exceeds the levels required to inhibit K_{ATP} channels at pancreatic, cardiac, and vascular tissues. Tolbutamide and repaglinide may

have partial selectivity for pancreatic receptors because the C_{SS} for these drugs is in the midst of reported IC_{50} values for the three receptor isoforms.

The tissue-specific molecular structure of the K_{ATP} channel likely accounts for observed differences in tissue selectivity reported for insulin secretagogues. For example, K_{ATP} channels in pancreatic β-cells are composed of the Kir6.2 and SUR1 subunits, whereas cardiac myocyte K_{ATP} channels contain Kir6.2 and SUR2A subunits and vascular smooth muscle K_{ATP} channels contain Kir6.1 and SUR2B subunits. Insulin secretagogues can be classified according to their binding to specific sites (A-, B- or AB-) in the SUR and Kir6.x subunits (Figure 2-1B, C). As all K_{ATP} channel isoforms contain either Kir6.1 or Kir6.2 subunits, drugs that bind to the B-site located in these subunits will likely display less tissue selectivity. In contrast, drugs that bind exclusively to the A-site in SUR subunit isoforms show a higher degree of tissue specific expression. Indeed, A-site drugs, like gliclazide and nateglinide, demonstrate greater K_{ATP} channel isoform selectivity with respect to SUR1 when compared to the AB-site drugs, like glyburide and glimepiride, and the B-site drug, repaglinide.

Differences in the tissue-specific K_{ATP} channel inhibitory properties amongst insulin secretagogues could have important clinical implications. When given at usual therapeutic doses, non-selective insulin secretagogues would inhibit K_{ATP} channels in heart tissue and likely negate the cardioprotective effects of K_{ATP} channel activation. This in turn would impede ischemic conditioning and possibly create a greater risk of adverse cardiovascular effects compared to pancreas-selective insulin secretagogues. Indeed, it is intriguing that glyburide, a non-selective insulin secretagogue, is commonly used in animal models to abolish ischemic conditioning, whereas gliclazide, a pancreas-selective insulin secretagogue, does not appear to affect ischemic conditioning.[108,189] Although the exact role of ischemic conditioning during a myocardial infarction in humans is not fully understood, observations from our study and others would suggest choice of insulin secretagogue may affect the outcome of these events in patients with type 2 diabetes.[108]

Concerns about the cardiovascular safety of insulin secretagogues were initially raised when the UGDP investigators reported a higher rate of cardiovascular events in tolbutamide users compared to placebo.[49]

Subsequently, several groups have examined the potential association between insulin secretagogues and adverse cardiovascular events, with conflicting results.[66,69–72,124,134,143–148,190–198] Most of these studies grouped insulin secretagogues as either one drug class[64,66,71,72,134,143,190,193] or two subgroups.[70,144,195] In the latter approach, insulin secretagogues were grouped by generation or by new versus old sulfonylureas rather than by differences in tissue selectivity or A-, B- or AB-site binding site designation (Figure 2-1C). Although three studies examined the risk of cardiovascular events associated with individual insulin secretagogues, these studies examined the risk relative to placebo or metformin.[64,192,198] Therefore, it is difficult to directly compare the cardiovascular effects of insulin secretagogues in these studies. The remaining studies compared the risk of cardiovascular events between individual insulin secretagogues or between pancreatic-selective and non-selective insulin secretagogues.[124,194,196,197] Generally, glyburide use was associated with a higher risk of all cause and cardiovascular-related mortality compared to gliclazide. However, most of these associations were not statistically significant, likely because of the small sample sizes or limited number of events. Although findings from these studies may suggest a safer cardiovascular profile with the pancreas-selective (A-site) drug gliclazide compared to the non-selective (AB-site) drug glyburide, future studies are required to explore this association.

Results from this systemic review should be viewed with some caution, because several assumptions were made. First, the C_{SS} calculated in this study is for plasma rather than tissue-specific concentrations, the latter of which are not available in humans. We assumed that plasma C_{SS}, our only measure of systemic exposure to insulin secretagogues, would be a reasonable proxy measure for drug concentration at the site of action. The reliability of this assumption is strengthened by the fact that none of the drugs possesses a particularly high value of oral volume of distribution. Indeed, all volumes of distribution are less than total body water, which increases the likelihood that the plasma C_{SS} accurately reflects concentration at the site of action. Any error imparted by this assumption would likely result in an overestimation of actual concentrations at the site of action. For example, the nonsteroidal anti-inflammatory drug etodolac is acidic, with high plasma protein binding and low

volume of distribution, like the sulfonylureas. In animal models, tissue concentrations of etodolac are generally lower than plasma.[199]

Second, many of the cited experiments examined animal tissues and cloned K_{ATP} channels expressed in cell lines rather than primary human tissue samples. Although these are accepted models for examining pharmacological activities, there may be some uncontrolled factors that could affect the actual IC_{50} values in human tissue. Moreover, there may be other unexpected differences between in vivo and in vitro activity of the sulfonylureas. For example, there are some animal data to suggest glimepiride does not inhibit cardiac ischemic conditioning.[200]

Third, data for some insulin secretagogues were combined from different experimental conditions to garner a complete picture of affinity to the three SUR isoforms. The two patch- clamp techniques used by most studies are different in some respects, especially regarding the site of drug application (outside the cell membrane in the whole-cell technique vs. inside the membrane in the inside–out technique). In addition, the presence or absence of intracellular nucleotides is known to alter the inhibitory effect of sulfonylureas.[188] Although these differences in experimental conditions probably explain some of the variations in IC_{50} values observed for the same SUR isoform and the same insulin secretagogue, we believe these data are reasonably comparable. All studies were recorded under steady-state conditions and sulfonylureas readily cross the cell membrane. In addition, the IC_{50} value is a ratio of channel conductance in the presence of drug relative to the same experimental condition in the absence of drug.

Finally, other factors, such as the impact of different sulfonylureas on atherosclerosis and the risk of hypoglycemia, may also contribute to variations in the clinical effects of insulin secretagogues beyond their action on SUR isoforms.[109,201,202]

Conclusions

In conclusion, insulin secretagogues appear to have different tissue selectivity characteristics at usual therapeutic doses. Although these different characteristics can be explained by the known structure activity relationships and binding site designations of these drugs, our proposed classification of tissue

selectivity should be treated with some caution because it is based on the assumption that plasma C_{SS} is a reasonable proxy measure for drug concentration at the site of action. If true, differences in tissue selectivity could translate into different levels of cardiovascular risk. Future studies examining the association between insulin secretagogues and adverse cardiovascular events should consider these characteristics.

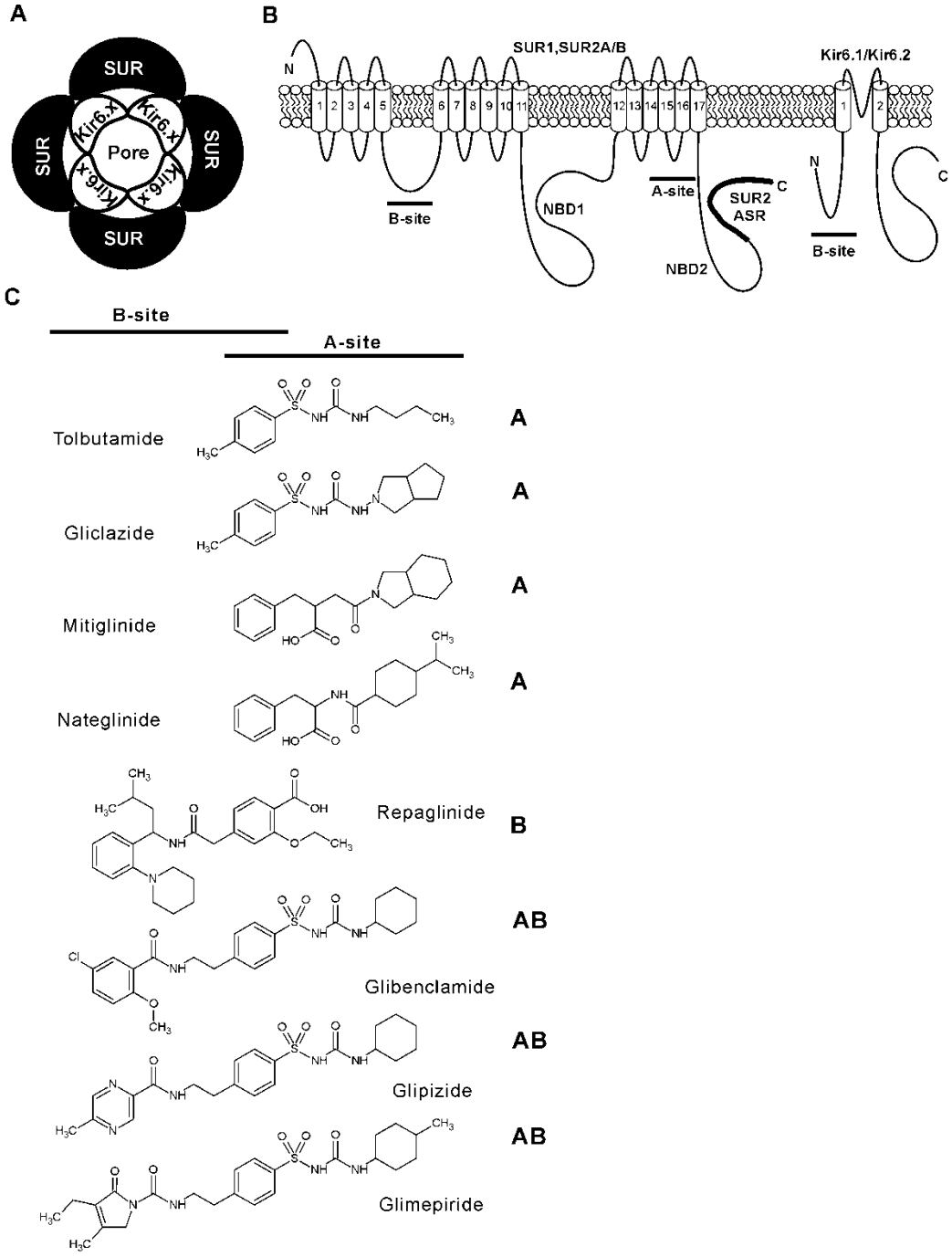
Table 2-1. Characteristics of studies included the systematic review

Study	*Sulfonylurea Receptor (SUR) protein source*			*K_{ATP} channel protein source*	*Cell line*	*Patch-clamp technique*	*Drugs investigated*
	SUR1 (β-cell)	*SUR2A (myocyte)*	*SUR2B (VSM)*	*Kir6.2/Kir6.1*			
Stephan, 2006[187]	Rat	Mouse	Mouse	Mouse	HEK 293T	I/O, WC	Glyburide, Repaglinide
Chachin, 2003[164]	Mouse	Mouse	Mouse	Mouse	HEK 293T	I/O	Nateglinide
Reimann, 2003[182]	Rat	Rat	Rat	Mouse	XLO	I/O	Meglitinide
Hansen, 2002[174]	Human	-	-	Human	HEK 293T	WC	Nateglinide, Repaglinide
Proks, 2002[180]	Rat	-	-	Mouse	XLO	I/O	LY389382, LY397364, Midaglizole
Lawrence, 2002[177]	-	NS	-	NS	HEK 293T	O/O	Glimepiride
Manning Fox, 2002[179]	Ins-1	Rabbit, Rat	-	Mouse	COS-1, TSA20	I/O, WC	Hmr 1098
Hu, 2002[176]	Rat	-	-	-	-	WC	Glyburide, Nateglinide, Repaglinide
Dabrowski, 2001[165]	Rat	Rat, Human	Rat, Human	Mouse, Human	XLO, HEK 293T	I/O, WC	Repaglinide
Song, 2001[186]	Rat	Rat	Rat	Mouse	XLO	I/O	Glimepiride
Reimann, 2001[181]	Rat	Rat	Mouse	Mouse	XLO	I/O	Mitiglinide
Hambrock, 2001[173]	-	-	Mouse	Mouse	HEK 293T	WC	Glyburide
Sunaga, 2001[185]	Human, Hamster	Rat	Rat	Human, Mouse	COS-1	I/O	Mitiglinide
Russ, 2001[183]	Rat	Mouse	Mouse	Mouse	HEK 293T	I/O, WC	Glyburide, HMR 1883
Lawrence, 2001[178]	Mouse	Rat	Rat	-	-	WC	Gliclazide, Glyburide
Gopalakrishnan, 2000[169]	Human	-	-	Human	HEK 293T	WC	Glyburide
Gribble, 1999[171]	Rat	Rat	Rat	Mouse	XLO	I/O	Gliclazide, Glimepiride
Dorschner, 1999[166]	Hamster	Rat	Rat	Mouse	COS-7	I/O, WC	Glipizide, Glyburide, Meglitinide, Tolbutamide
Hu, 1999[175]	Rat	Rat	Rat , Porcine	-	-	WC	Glyburide, Nateglinide, Repaglinide

Study	*Sulfonylurea Receptor (SUR) protein source*			*K_{ATP} channel protein source*	*Cell line*	*Patch-clamp technique*	*Drugs investigated*
	SUR1 (β-cell)	*SUR2A (myocyte)*	*SUR2B (VSM)*	*Kir6.2/Kir6.1*			
Giblin, 1999[168]	Hamster	-	-	NS	HEK 293T	I/O	Tolbutamide
Gribble, 1998[188]	Rat	Rat	-	Mouse	XLO	I/O	Glyburide, Meglitinide, Tolbutamide
Babenko, 1998[162]		Human	-	Human	COSm6	I/O	Tolbutamide
Gribble, 1997[203]	Rat	-	-	Mouse	XLO	I/O	Tolbutamide
Barrett-Jolley R, 1997[163]		Rat*	-	-	-	I/O	Glyburide
Gromada, 1995[172]	Rat	-	-	-	-	WC	Glyburide, Repaglinide
Schwanstecher, 1994[184]	Mouse	-	-	-	-	WC	Glimepiride
Findlay, 1992[167]	-	Guinea pig	-	-	-	WC	Glyburide, Tolbutamide

*Flexor digiorum muscle was used
HEK: human embryonic kidney cell, I/O: inside-out, INS-1: rat insulinom cell, K_{ATP}: ATP-sensitive potassium, NS: not specified, O/O: outside-out, SUR: sulfonylurea receptor, VSM: vascular smooth muscle, WC: whole cell, XLO: *Xenopus Laevis* oocyte

Figure 2-1. Structure and molecular makeup of K_{ATP} channel and designated binding sites of insulin secretagogues



A. 4 SUR and 4 Kir6.x subunits co-assemble to form the functional hetero-octameric K_{ATP} channel complex. **B**. Molecular makeup of K_{ATP} channels assembled from SUR and Kir6.2 subunits. Nucleotide binding domains (NBDs) 1 and 2 as well as the A-/B- binding sites for pharmacological inhibitors are indicated. There are two isoforms of SUR: SUR1 and SUR2. SUR2A and SUR2B are splice variants that are identical except for the distal C-terminal alternative splicing region (SUR2 ASR). **C**. Structures and A-,B- and AB-binding site designations for the drugs investigated in this study.

Figure 2-2. Citations flow diagram

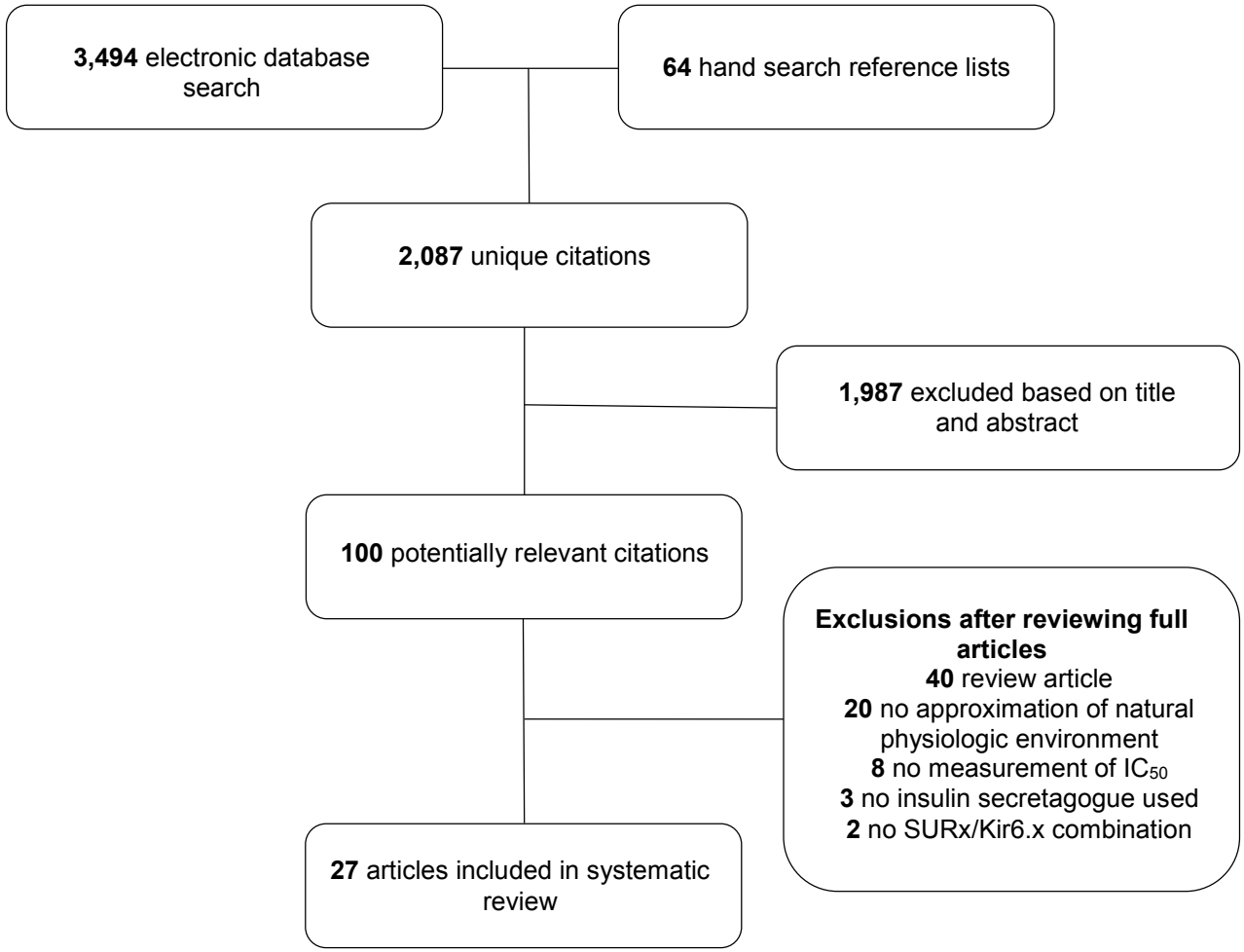
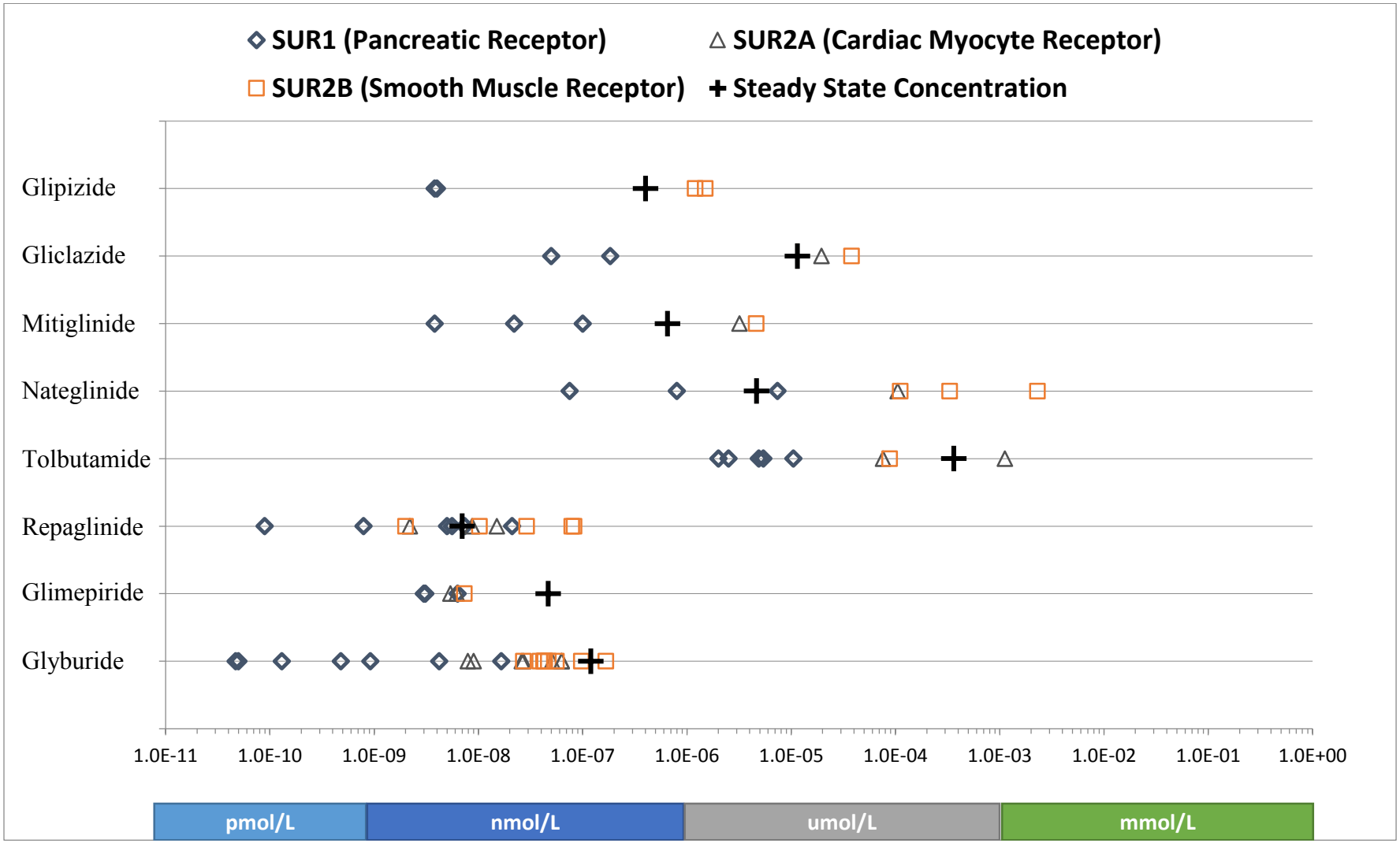


Figure 2-3. Half-maximal inhibitory concentration (IC_{50}) for K_{ATP} channels in the pancreas, cardiac myocyte, and vascular smooth muscle and steady state plasma concentration (C_{SS}) for insulin secretagogues (scaled to log-format)



CHAPTER 3

Risk of Acute Coronary Events Associated With Glyburide Compared to Gliclazide Use in Patients with Type 2 Diabetes: A Nested Case-Control Study[2]

3.1. Abstract

Background

Sulfonylureas might increase the risk of adverse cardiovascular events; however, emerging evidence suggests there may be important differences amongst these drugs. Some, like glyburide, inhibit ATP-sensitive potassium (K_{ATP}) channels in the heart and pancreas, while others, like gliclazide, are more likely to selectively inhibit K_{ATP} channels in the pancreas. We hypothesized that the risk of acute coronary syndrome (ACS) events would be higher in patients using glyburide compared to gliclazide.

Methods

This nested case-control study used administrative healthcare databases from Alberta, Canada. New users of glyburide or gliclazide aged ≥66 years between 1998-2010 were included. Cases were individuals with an ACS-related hospitalization or death. Up to 4 controls were matched on birth year, sex, cohort-entry year, and follow-up time. Multivariable conditional logistic regression was used to estimate adjusted odds ratios (OR), controlling for baseline drug use and comorbidities.

[2] A version of this chapter has been published as *Abdelmoneim A, Eurich D, Gamble J, Johnson J, Seubert J, Qiu W, et al. Risk of acute coronary events associated with glyburide compared with gliclazide use in patients with type 2 diabetes: a nested case-control study. Diabetes Obes Metab. 2014;16(1):22–9*. Permission to reuse this copyrighted material was provided by the publisher, John Wiley and Sons, License Number 3678870554680.

Results

Our cohort included 7,441 gliclazide and 13,884 glyburide users; 51.4% men, mean (standard deviation; SD) age 75.5 (6.6) years and mean (SD) duration of follow-up 5.5 (4.0) years. A total of 4,239 patients had an ACS-related hospitalization or death and were matched to 16,723 controls. Compared to gliclazide use, glyburide use was associated with a higher risk (adjusted odds ratio (OR) 1.14; 95% confidence interval (CI) 1.06-1.23) of ACS-related hospitalization or death over 5.5 years (number needed to harm 50).

Conclusion

In this observational study, glyburide use was associated with a 14% higher risk of ACS events compared to gliclazide use. Although the difference is small and likely to have implications at the population level rather than the individual patient or clinician, any causal inferences regarding sulfonylurea use and adverse cardiovascular risk should be tested in a large-scale randomized controlled trial.

3.2. Introduction

It is well known that sulfonylureas lower blood glucose and reduce the risk of microvascular complications associated with diabetes.[64] There is ongoing debate, however, that these drugs increase the risk of adverse cardiovascular events. Questions about the cardiovascular safety of sulfonylureas arose in the 1970s, when the UGDP reported a significantly higher rate of cardiovascular-related death in patients using tolbutamide compared to placebo.[49] In contrast, the UKPDS showed a similar risk of death or myocardial infarction for patients using glyburide or chlorpropamide compared to controls.[64] Additionally, several observational studies have examined the potential association between sulfonylureas and adverse cardiovascular events. However, there has not been a consistent message from these studies, with some observing a higher risk,[65–67,134,146] some observing a lower risk,[69] and others observing no differences.[70–72,145,204] The debate continues, with additional questions about possible differences amongst individual sulfonylureas.[196,205]

Sulfonylureas promote insulin release from pancreatic β-cells by binding to sulfonylurea receptors and inhibiting K_{ATP} channels.[138] In cardiac myocytes and smooth muscle cells, however, activation of K_{ATP} channels play an integral role in ischemic conditioning: an endogenous protective mechanism in which brief episodes of ischemia and reperfusion enable cardiac tissue to be more resilient during a more profound ischemic insult.[106,107,132] Although sulfonylurea-mediated inhibition of pancreatic K_{ATP} channels produces a desired therapeutic effect, additional inhibition of K_{ATP} channels in the heart may contribute to adverse cardiovascular effects.[108,129,206] Interestingly, there are important differences among sulfonylureas in their tissue-specific binding affinities, whereby glyburide might inhibit K_{ATP} channels in the heart to a larger degree than gliclazide.[205]

In this study, we compared the risk of adverse cardiovascular events between type 2 diabetic patients using glyburide or gliclazide as their sole sulfonylurea. We hypothesized that glyburide, a drug that is more likely to inhibit K_{ATP} channels in both the heart and pancreas, would be associated with a higher

risk of adverse cardiovascular events compared to gliclazide, a drug that appears to be pancreas-selective.

3.3. Methods

Population & settings

This population-based, nested case-control study used administrative healthcare data of Alberta Health (Alberta, Canada). Under provincially funded programs, all Alberta residents receive coverage for hospitalizations, emergency department visits, and physician services. Albertans aged ≥ 65 years also receive partial coverage (30% co-payment to a maximum of $25) for prescription medications. The administrative healthcare databases used to manage these programs are linkable and have been used extensively in previous epidemiologic studies because of the high level of accuracy and completeness of data.[207–211] In brief, the Discharge Abstract Database records information on hospital admissions; the Ambulatory Care database contains emergency department visits; the Practitioner Payments database captures office-based visits; the Alberta Vital Statistics database contains information on birth and death records; and the Population Registry file contains demographic information. The Alberta Blue Cross (ABC) medication database captures dispensation claim information for individuals aged ≥ 65 years.

Alberta residents aged 66 years and older with prescription drug coverage from ABC were eligible for cohort entry. We included all new users of gliclazide or glyburide, the two most commonly prescribed sulfonylureas in Alberta, between January 1998 and December 2010. New users were identified using a 1-year washout period of no dispensation for any oral antidiabetic drug or insulin. The cohort entry date was defined as the first dispensation date for glyburide or gliclazide. Baseline characteristics were identified from administrative healthcare databases up to 1 year prior to the cohort entry date. All patients were followed from the cohort entry date until reaching the outcome, death from any cause, leaving the province, switching to another sulfonylurea or December 2010. The University of Alberta Health Research Ethics Board approved the study protocol (Appendix C).

Case definition and control selection

Cases were defined as individuals who were hospitalized or died because of an ACS event. The hospitalization or death was considered attributable to an ACS event if there were International Classification of Diseases (ICD) codes for myocardial infarction or unstable angina (Appendix D).[212–214] We also included procedure codes for percutaneous coronary intervention since this revascularization procedure is a recommended treatment for ACS events.[215,216] Individuals who experienced more than 1 event (i.e., were hospitalized and died because of an ACS event) were only counted once. Therefore the event date for each case was defined as the hospital admission date, revascularization procedure date, or date of death, whichever occurred earliest. Controls were selected using risk-set sampling.[217,218] To be considered eligible as a control within each risk set, a patient must have the same duration of follow-up as the case, but still be "at risk" for the outcome of interest (i.e., actively followed, alive, and event free); therefore, a patient could be a control patient for several cases.[218] A pool of "at risk" patients was established for each case and we randomly selected up to 4 controls matched on sex, birth year, and cohort entry year. The case and control selection methods were repeated for ACS-related hospitalization and ACS-related death separately, using an identical procedure.

Exposure assessment

Sulfonylurea exposure was based on dispensation records prior to the event date. As others have done previously,[122] we initially defined sulfonylurea exposure at the cohort entry date. However, we were also interested in determining exposure status in the weeks prior to the event. We observed that the median duration of days supplied for glyburide and gliclazide was 90 days, which is consistent with the provincial policy to provide a 100-day supply for diabetes drugs. Allowing for an average adherence rate of 80%, we assumed a supply of glyburide or gliclazide could last up to 120 days.[219] Thus, we stratified our analyses by grouping patients dispensed a supply of glyburide or gliclazide within 120 days prior to the event date as "recent exposure" and patients dispensed a supply more than 120 days before the event date as "past exposure".

Covariates

Dispensation records from the ABC database were used to determine if patients were using an antihypertensive drug, digoxin, platelet inhibitor, oral anticoagulant, lipid lowering agent, hormone replacement therapy or COX-II inhibitors within one year before the cohort entry date. Other oral antidiabetic drugs or insulin were considered for patients starting on a combination therapy. We used physician visit, emergency department visit and hospitalization records within one year before the cohort entry date to identify a pre-defined list of comorbid conditions as well as hospitalizations or emergency department visits for hypoglycemia. Comorbid conditions were included in the regression model as a comorbidity score.[220] To control for possible differences in management of patients using glyburide compared to gliclazide, we identified physician service codes for guideline concordant procedures, such as retinopathy screening, lipid blood glucose, and renal function assessment; mammography and bone mineral densitometry screening.[54]

Statistical analyses

Descriptive statistics were calculated for baseline characteristics to compare patients using gliclazide and glyburide at cohort entry and to compare cases and controls for each outcome. Between group differences were measured using chi-square or Student's t-tests, as appropriate.

We used conditional logistic regression analyses to estimate the unadjusted and adjusted OR and 95% CI for each outcome associated with glyburide compared to gliclazide use (reference group). All first order interactions between sulfonylurea exposure and each covariate were examined, with none achieving statistical significance ($p>0.05$ for all). We used the variance inflation factor (VIF) with a cut-off of 10 to determine if there was multicollinearity amongst variables.[221] All VIFs ranged from 1.00 to 1.23, which suggested multicollinearity was unlikely and therefore we retained all variables in the adjusted models. All analyses were conducted using Stata 12 (StataCorp LP, College Station, TX, USA).

Sensitivity analyses

First, we conducted an analysis using the entire risk set for each case rather than randomly selecting 4 controls for each case. Second, we tested the effect of our assumptions for recent or past exposure by using 36 days (1 month drug supply + 80% adherence rate) and 365 days prior to the event date to stratify patients as recent or past exposure. Third, we repeated our matching and analysis using the cohort of prevalent gliclazide and glyburide users. Fourth, we excluded patients who were hospitalized during the exposure assessment window because they might be misclassified as being not exposed.[222] Last, we conducted a propensity score adjusted analysis. The propensity score modeled the probability of glyburide versus gliclazide use given all other study covariates at cohort entry. The propensity scores were grouped into quintiles and used as adjustment covariates in the regression model.[223]

To assess the robustness of our model, we compared the difference in risk of a hospitalization or death for pneumonia between patients using glyburide and gliclazide. There is no plausible association between ischemic conditioning and risk of pneumonia and no reported associations between sulfonylurea use and risk of pneumonia. We expected to observe no difference in pneumonia risk between these drugs.

Estimate of number needed to harm (NNH)

We used the formula described by the Center for Evidence Based Medicine to estimate the number of additional patients using glyburide for one more patient to suffer a hospitalization or death attributable to an ACS event.[224] The control event rate was estimated as the number of ACS events in patients using gliclazide between 1998 - 2010. The number needed to harm was then calculated using the adjusted odds ratio in the following formula:

$$NNH = (((CER*(OR-1)) + 1) / ((CER*(OR-1)*(1-CER))$$

NNH: number needed to harm, CER: control event rate, OR: odds ratio

3.4. Results

Study cohort

We identified 7,441 gliclazide users and 13,884 glyburide users as their sole sulfonylurea during the observation period (Figure 3-1). There were 10,970 (51.4%) men; mean (SD) age was 75.5 (6.6) years and mean duration of follow-up was 5.5 (4.0) years. A total of 4,028 patients had an ACS-related hospitalization and 846 patients died from an ACS-related event. Table 3-1 contains baseline characteristics of the study cohort according to gliclazide or glyburide use.

ACS-related hospitalization or death

The 4,239 cases with an ACS-related hospitalization or death were matched (4,163 [98.2%] fully matched) to 16,723 controls (Table 3-2). Twenty cases were excluded because they were not matched to any controls. Baseline prevalence of digoxin, antihypertensive, lipid lowering, antiplatelet, anticoagulant and other antidiabetic drugs was higher amongst cases compared to controls. Similarly, comorbid conditions were more prevalent at baseline amongst cases compared to controls.

Compared to gliclazide, glyburide users had a higher risk of an ACS-related hospitalization or death after adjusting for baseline drug use and comorbidities (adjusted OR 1.14, 95% CI 1.06 – 1.23; p=0.001; Figure 3-2). When stratified by timing of last dispensation, recent glyburide exposure was associated with a higher risk of ACS-related hospitalization or death compared to recent gliclazide exposure (adjusted OR 1.13; 95% CI 1.04 – 1.24; p=0.007). A similar association was observed in patients with past glyburide exposure compared to those with past gliclazide exposure (adjusted OR 1.16; 95% CI 1.01 – 133; p=0.036).

Results from all sensitivity analyses were consistent in direction, magnitude, and statistical significance with the main analysis (Figure 3-3).

ACS-related hospitalization

A total of 4,010 cases of ACS-related hospitalization were matched to 15,833 controls (Table 3-2), with 18 cases excluded because they were not matched to any controls. After adjustment for covariates, glyburide users had a higher risk of ACS-related hospitalization compared to gliclazide users (adjusted OR 1.14; 95% CI 1.06 – 1.24; p=0.001; Figure 3-2). Recent exposure to glyburide was associated with a significantly higher risk of ACS-related hospitalization compared to recent gliclazide exposure (adjusted OR 1.15; 95% CI 1.05 – 1.26; p=0.003). In contrast, the risk of ACS-related hospitalization was similar between patients with past exposure to glyburide and patients with past exposure to gliclazide (adjusted OR 1.13; 95% CI 0.98 – 1.30; p=0.10).

ACS-related death

We were able to match 791 ACS-related deaths to 3,103 controls (Table 3-2). After adjustment for covariates, glyburide users had a similar risk of ACS-related death (adjusted OR 1.14; 95% CI 0.95 – 1.36; p=0.16; Figure 3-2) compared to gliclazide users. Stratification by timing of the last dispensation showed that recent exposure to glyburide had a similar risk of ACS-related death compared to recent gliclazide exposure (adjusted OR 1.02; 95% CI 0.81 – 1.29; p=0.88); whereas, the risk was significantly higher in patients with past exposure to glyburide compared to past gliclazide exposure (adjusted OR 1.32; 95% CI 1.00 – 1.75; p=0.046).

Pneumonia-related hospitalization or death

There was no significant difference in the risk of hospitalization or death for pneumonia between glyburide and gliclazide users (adjusted OR 1.05; 95% CI 0.96 – 1.15; p=0.26).

Number needed to harm

Our cohort included 7,441 gliclazide users, with 1,330 (17.9%) experiencing an ACS-related hospitalization or death during a mean follow-up of 5.5 years. With this control event rate and considering an adjusted OR of 1.14, we estimated that 50 patients would have to be treated with glyburide for 5.5 years for one additional ACS event to occur compared to gliclazide.[225]

3.5. Discussion

Between 1998 - 2010, 21,325 patients used either glyburide or gliclazide as their sole sulfonylurea for a mean follow-up period of 5.5 years. Overall, glyburide users had a small, but significantly higher risk of ACS-related hospitalization or death compared to gliclazide users. We estimated that an additional 50 patients would need to be treated with glyburide for one more patient to be harmed. Although this NNH may not impact decisions at the individual clinician or patient level, it may have important implications for decisions about which sulfonylurea to recommend at the population level.

When given at usual therapeutic doses, glyburide inhibits K_{ATP} channels in both the heart and pancreas, while gliclazide is more likely to selectively inhibit K_{ATP} channels in the pancreas.[205] Inhibition of K_{ATP} channels in the heart will impede ischemic conditioning and has resulted in increased myocardial damage in animal models.[108,125] Our observation that glyburide users had a higher risk of cardiovascular events compared to gliclazide users is consistent with this phenomenon. Although there is limited human data of ischemic conditioning, Muller and colleagues observed that patients with angina episodes in the week preceding hospitalization for a myocardial infarction had a more favorable short-term prognosis compared to those without prior angina. They hypothesized that antecedent angina episodes may contribute to myocardial conditioning.[141] If sulfonylureas impair ischemic conditioning they must be at the site of action, the K_{ATP} channels in the heart, during the weeks prior to the event; therefore timing of sulfonylurea exposure in relation to the cardiovascular event is an important consideration.[107,121] Recent exposure to glyburide would abolish the protective mechanism of antecedent angina episodes, while past exposure would likely have no effect. Indeed, we observed a significantly higher risk of ACS-related hospitalization or death in patients recently exposed to glyburide compared to those recently exposed to gliclazide. In contrast, the risk of ACS-related hospitalization was similar in patients with past exposure to glyburide compared to those with past exposure to gliclazide.

Sulfonylureas may have other cardiovascular effects beyond impairment of ischemic conditioning, including antiplatelet, antiarrhythmic, or antioxidant

properties.[226–228] Additionally, sulfonylurea-induced hypoglycemia could precipitate QT-prolongation and ischemia.[103,105] Regardless of the underlying biological mechanism explaining the harmful cardiovascular effect of sulfonylureas, it is important to examine the sulfonylureas separately rather than as one drug class. Grouping sulfonylureas may introduce confounding, especially if a patient uses more than 1 sulfonylurea during the observation period. Some observational studies have directly compared individual sulfonylureas or grouped sulfonylureas according to tissue-specific activity with inconsistent results.[122,124,194,196,197,204,229] Differences in study population, outcome selection, sulfonylurea exposure definition, and analytic approach, as well as small sample size or low number of events may explain why some of these studies did not find statistically significant differences between glyburide and other sulfonylureas.[194,197,229] Our study used population-based health databases containing a large group of patients using the two sulfonylureas of interest and observed a relatively high rate of events over a 12-year period. Moreover, the case-control study design allowed us to restrict our exposure definition to the weeks leading up to the ACS event.

There are important limitations to consider when interpreting our findings. First, like other observational studies, there are inherent design elements that limit our conclusions to an association and not causation. The hypothesis that glyburide use is more likely to cause adverse cardiovascular events than gliclazide use should be tested in a properly designed randomized controlled trial. Second, we lacked clinical data, such as blood pressure, lipid levels, HbA_{1c}, waist circumference, or smoking status. Although we accounted for the presence of diagnosed or treated conditions (for example, hypertension or use of antihypertensive drugs) in the multivariate analyses, we cannot rule out the possibility that the observed risk difference between glyburide and gliclazide use is due to residual confounding. Third, as with all observational studies, we assumed a dispensation record was a reasonable indicator for exposure. This indirect measurement would overestimate exposure status if patients obtained a supply of drugs and then never consumed them. We believe, however, that this misclassification of exposure would be non-differential between gliclazide and glyburide. Fourth, use of either glyburide or gliclazide was not randomly

allocated; therefore, selection bias may be present. It is possible that cost (generic formulations of gliclazide were not available until 2004), risk of hypoglycemia, patient age, or renal function influenced the decision to use a specific sulfonylurea. However, a propensity score-adjusted analysis produced similar results. Finally, we were not able to assess the cardiovascular risk of other sulfonylureas because less than 5% of patients were using them.

Conclusions

In conclusion, we observed a statistically significant 14% higher risk of ACS among patients using glyburide compared to those using gliclazide. Due to the inherent limitations of observational studies, any causal inferences about the difference in cardiovascular risk amongst sulfonylureas should be tested in a large-scale randomized controlled trial. Until that study is completed, the clinical importance of our observed risk difference may have more implications at the population level rather than at the individual patient level.

Table 3-1. Baseline characteristics for the full cohort by sulfonylurea use

	Gliclazide (n=7,441)	***Glyburide (n=13,884)***
Age, mean (SD), years	75.5 (6.7)	75.4 (6.5)
Men	3,882 (52.2%)	7,088 (51.1%)
Duration of follow up, mean (SD), years	5.4 (4.1)	5.5 (4.0)
Antidiabetic drugs		
Metformin	1,609 (21.6%)	3,446 (24.8%)*
Thiazolidinediones	75 (1.0%)	58 (0.4%)*
Acarbose	91 (1.2%)	144 (1.0%)
Insulin	36 (0.5%)	66 (0.5%)
Other drugs		
Antihypertensive agents	4,678 (62.9%)	7,940 (57.2%)*
Lipid lowering drugs	1,711 (23.0%)	2,105 (15.2%)*
Digoxin	670 (9.0%)	1,157 (8.3%)
Antiplatelet drugs	172 (2.3%)	207 (1.5%)*
Anticoagulant drugs	609 (8.2%)	898 (6.5%)*
Hormone replacement therapy	301 (4.1%)	480 (3.5%)*
COX-2 Inhibitors	545 (7.3%)	606 (4.4%)*
Comorbid conditions		
Ischemic heart disease	1,380 (18.6%)	2,407 (17.3%)*
Congestive heart failure	900 (12.1%)	1,440 (10.4%)*
Cardiac arrhythmia	720 (9.7%)	1,172 (8.4%)*
Valvular disease	209 (2.8%)	320 (2.3%)*
Pulmonary circulation disorder	119 (1.6%)	169 (1.2%)*
Cerebrovascular disease	414 (5.6%)	791 (5.7%)
Peripheral vascular disease	332 (4.5%)	527 (3.8)*
Hypertension	3,866 (52.0%)	6,544 (47.1%)*
Hyperlipidemia	420 (5.6%)	639 (4.6%)
Liver disease	92 (1.2%)	113 (0.8%)*
Renal failure	269 (3.6%)	323 (2.3%)*
Depression	625 (8.4%)	1,036 (7.5%)*
Hypoglycemia emergency room visit	71 (1.0%)	169 (1.2%)
Comorbidity score, median (IQR)	2 (1-3)	1 (1-3)*

*p<0.05
COX-2: cyclooxygenase-2, IQR: inter-quartile range; SD: standard deviation

Table 3-2. Baseline characteristics of cases and matched controls by study outcome

	Overall ACS event		*ACS-related hospitalization*		*ACS-related death*	
	Cases (n= 4,239)	***Controls (n=16,723)***	***Cases (n=4,010)***	***Controls (n=15,833)***	***Cases (n=791)***	***Controls (n=3,103)***
Age, mean (SD), years	75.7 (6.2)	75.6 (6.1)	75.6 (6.2)	75.5 (6.1)	77.8 (6.3)	77.6 (6.2)
Men	2,381 (56.2%)	9,417 (56.3%)	2,241 (55.9%)	8,869 (56.0%)	458 (57.9%)	1,801 (58.0%)
Antidiabetic drugs						
Metformin	992 (23.4%)	3,828 (22.9%)	936 (23.3%)	3,586 (22.7%)	187 (23.6%)	661 (21.3%)
Thiazolidinediones	5 (0.1%)	52 (0.3%)*	5 (0.1%)	41 (0.3%)	1 (0.1%)	7 (0.2%)
Acarbose	56 (1.3%)	173 (1.0%)	52 (1.3%)	140 (0.9%)*	13 (1.6%)	24 (0.8%)*
Insulin	24 (0.6%)	61 (0.4%)	23 (0.6%)	65 (0.4%)	1 (0.1%)	16 (0.5%)
Other drugs						
Antihypertensive agents	2,604 (61.4%)	9,009 (53.9%)*	2,470 (61.6%)	8,613 (54.4%)*	478 (60.4%)	1,679 (54.1%)*
Lipid lowering drugs	705 (16.6%)	2,460 (14.7%)*	671 (16.7%)	2,317 (14.6%)*	97 (12.3%)	393 (12.7%)
Digoxin	429 (10.2%)	1,079 (6.5%)*	392 (9.8%)	1,050 (6.6%)*	102 (12.9%)	252 (8.1%)*
Antiplatelet drugs	92 (2.2%)	210 (1.3%)*	90 (2.4%)	183 (1.2%)*	8 (1.0%)	34 (1.1%)
Anticoagulant drugs	315 (7.4%)	872 (5.2%)*	287 (7.2%)	855 (5.4%)*	72 (9.1%)	162 (5.2%)*
Hormone replacement therapy	125 (3.0%)	505 (3.0%)	125 (3.1%)	499 (3.2%)	16 (2.0%)	83 (2.7%)
COX-2 inhibitors	183 (4.3%)	698 (4.2%)	455 (3.4%)	387 (6.0%)*	82 (3.1%)	76 (6.1%)*
Comorbid conditions						
Ischemic heart disease	1,196 (28.2%)	2,375 (14.2%)*	1,129 (28.2%)	2,281 (14.4%)*	213 (26.9%)	489 (15.8%)*
Congestive heart failure	624 (14.7%)	1,226 (7.3%)*	579 (14.4%)	1,187 (7.5%)*	144 (18.2%)	249 (8.0%)*
Cardiac arrhythmia	428 (10.1%)	1,145 (6.9%)*	396 (9.9%)	1,099 (6.9%)*	88 (11.1%)	254 (8.2%)*
Valvular disease	129 (3.0%)	279 (1.7%)*	123 (3.1%)	262 (1.7%)*	26 (3.3%)	45 (1.5%)*
Pulmonary circulation disorder	68 (1.6%)	130 (0.8%)*	64 (1.6%)	119 (0.8%)*	13 (1.6%)	19 (0.6%)*
Cerebrovascular disease	293 (6.9%)	735 (4.4%)*	654 (4.9%)	296 (4.6%)	151 (5.7)	69 (5.5)
Peripheral vascular disease	252 (5.9%)	529 (3.2%)*	235 (5.9%)	479 (3.0%)*	59 (7.5%)	115 (3.7%)*
Hypertension	2,160 (51.0%)	7,757 (46.4%)*	2,061 (51.4%)	7,350 (46.4%)*	379 (47.9%)	1,461 (47.1%)
Hyperlipidemia	233 (5.5%)	715 (4.3%)*	222 (5.5%)	621 (3.9%)*	36 (4.6%)	112 (3.6%)
Liver disease	38 (0.9%)	111 (0.6%)	36 (0.9%)	82 (0.5%)*	5 (0.6%)	18 (0.6%)
Renal failure	129 (3.0%)	283 (1.7%)*	122 (3.0%)	272 (1.7%)*	23 (2.9%)	49 (1.6%)*
Depression	308 (7.3%)	1,023 (6.1%)*	285 (7.1%)	1,017 (6.8%)	60 (7.6%)	214 (6.9%)
Hypoglycemia ER visits	45 (1.1%)	153 (0.9%)	42 (1.1%)	148 (0.9%)	12 (1.5%)	37 (1.2%)
Comorbidity score, median (IQR)	2 (1-3)	1 (1-2)*	2(1-3)	1 (1-2)*	2(1-3)	1(1-2)*

*p<0.05

COX-2: cyclooxygenase-2, IQR: inter-quartile range, ER: emergency room, ACS: acute coronary syndrome; SD: standard deviation

Figure 3-1. Patient flow diagram

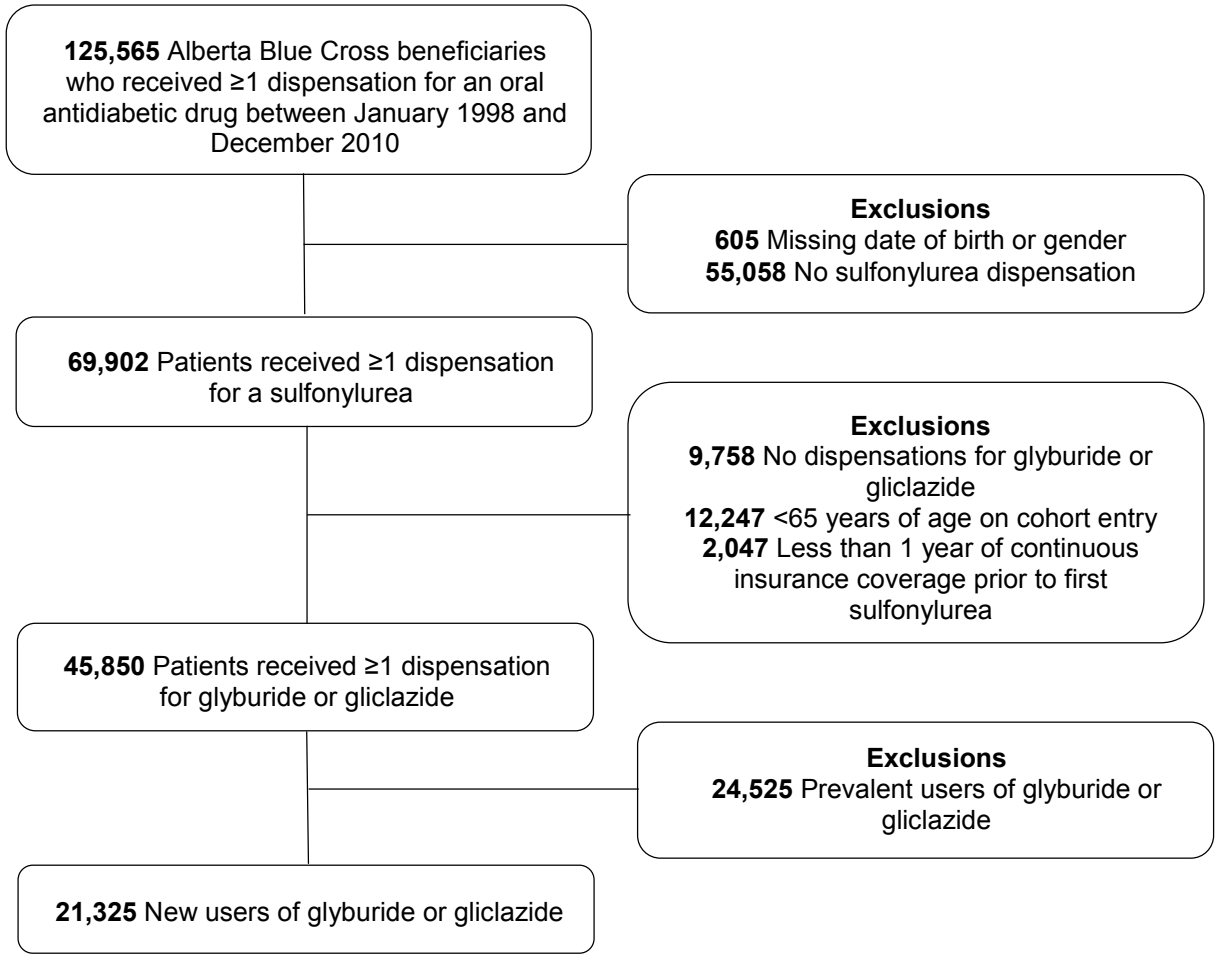
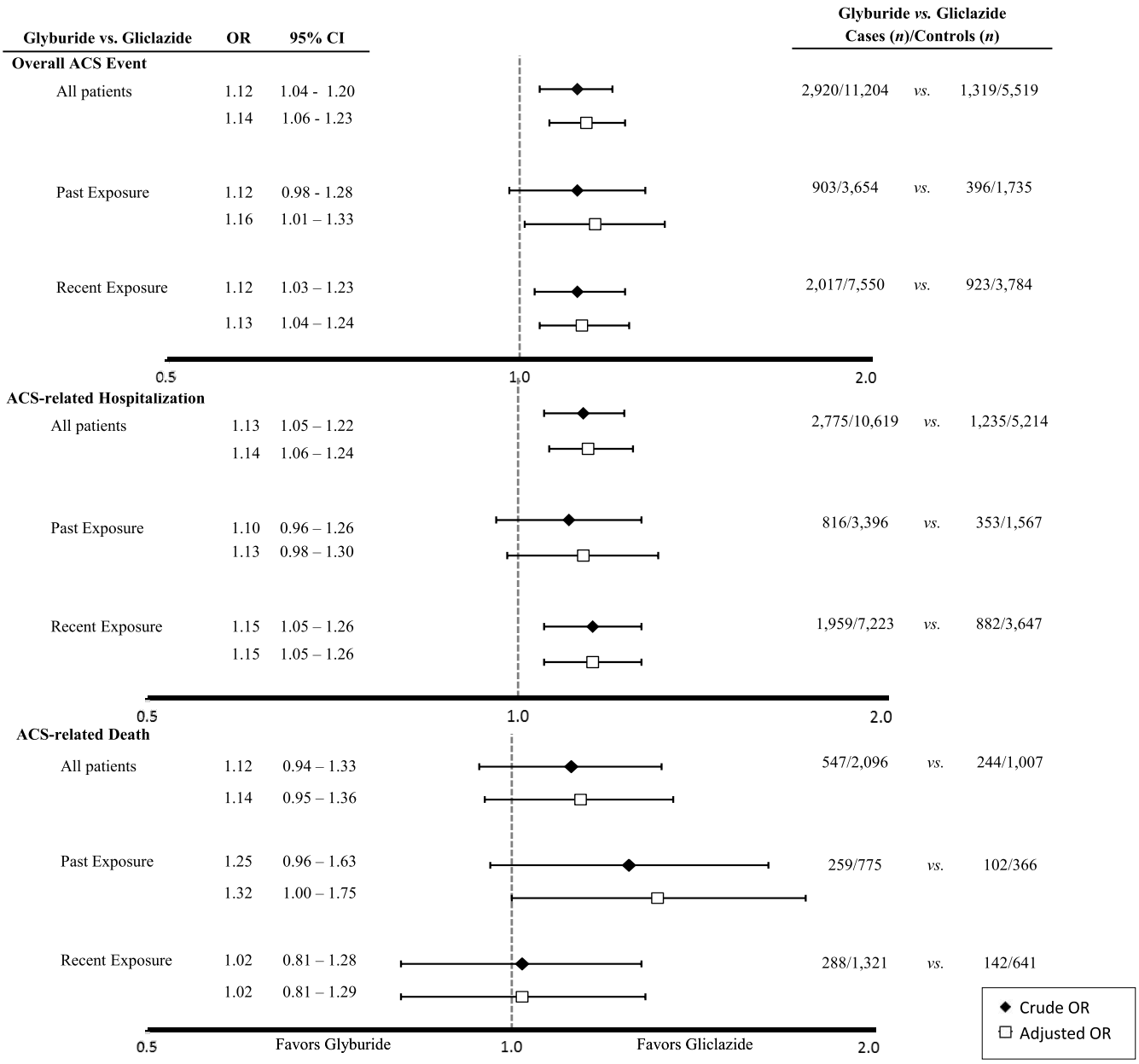
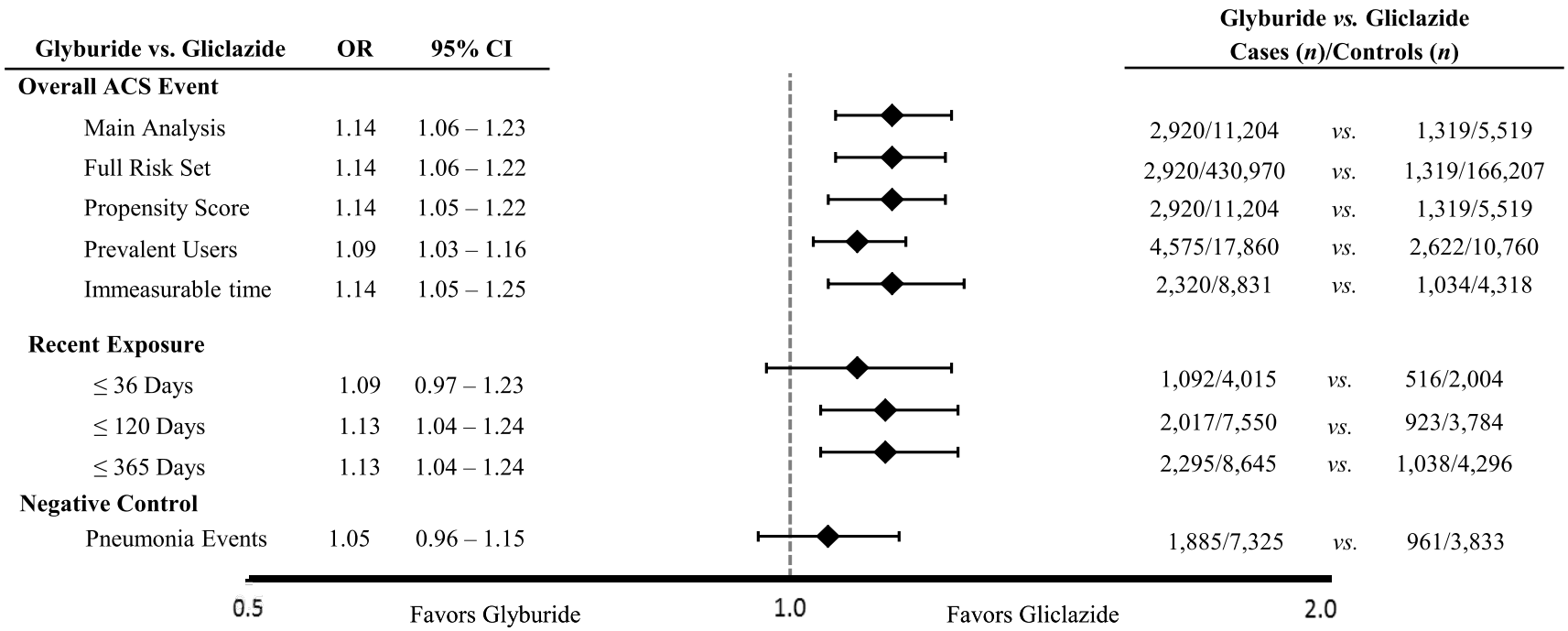


Figure 3-2. Crude and adjusted odds ratio of acute coronary syndrome events for glyburide and gliclazide users



ACS: Acute coronary syndrome, OR: odds ratio; CI: confidence interval
Adjusted OR: adjusted odds ratio for baseline drug use and comorbidities, Past exposure: a dispensation for glyburide or gliclazide more than 120 days of the event date, Recent Exposure: a dispensation for glyburide or gliclazide within 120 days of the event date

Figure 3-3. Sensitivity analysis adjusted odds ratio of acute coronary syndrome events for glyburide and gliclazide users



ACS: Acute coronary syndrome, OR: odds ratio; CI: confidence interval

CHAPTER 4

Dose-Response Relationship between Sulfonylureas and Major Adverse Cardiovascular Events in Elderly Patients with Type 2 Diabetes[3]

4.1. Abstract

Background

Recent evidence suggests sulfonylureas vary with respect to their cardiovascular risk profile. To further examine the possible causal relationship, the objective of this study was to determine if there is a dose-response relationship between sulfonylureas and adverse cardiovascular events.

Methods

Using administrative health databases from Alberta, Canada, we conducted a retrospective cohort study among elderly patients who received new dispensations for gliclazide or glyburide between 1998 and 2010. Patients were followed from their first dispensation until reaching a major adverse cardiovascular event (MACE) or censoring. A time-dependent variable was used to characterize exposure because dose can change during follow-up. Propensity-score adjusted Cox proportional hazard-regression models were used to compare between low (reference) and high dose groups.

Results

We identified 16,401 new users of gliclazide or glyburide (mean age (standard deviation; SD), 74.8 (6.6) years; males, 54.4%; and mean follow-up duration (SD), 2.6 (2.8) years). Among gliclazide users, MACE occurred with a similar

[3] A version of this chapter has been submitted for publication

rate within the low- and high-dose groups (34.0 and 36.5 per 1,000 person-years (PY), respectively; adjusted hazard ratio (HR) 1.14; 95% confidence interval [CI] 0.99–1.30, p=0.07). For glyburide users, however, MACE occurred less frequently in the low-dose group compared to the high-dose (38.2 and 43.1 per 1,000 PY, respectively; adjusted HR 1.18; 95% CI 1.02–1.36, p=0.02).

Conclusions

Among new users of sulfonylureas, there appears to be a dose-response relationship between glyburide and MACE. In contrast, there does not appear to be a dose-response relationship between gliclazide and MACE. These findings add further evidence that the cardiovascular risk varies among sulfonylureas.

4.2. Introduction

Sulfonylureas are a cornerstone in the management of type 2 diabetes, yet their cardiovascular safety is still controversial.[49,54,230] Observational study evidence suggests an increased cardiovascular risk with sulfonylureas,[76,77,81] while randomized controlled trial evidence suggests cardiovascular risk is not increased with sulfonylurea use.[78–80]

One possible explanation for the conflicting evidence from observational studies and randomized controlled trials is that sulfonylureas were often grouped as a one class.[50] There is growing evidence that there are important differences in the pharmacological properties among sulfonylureas. For example, gliclazide appears to selectively bind to pancreatic receptors, while glyburide is more likely to bind non-selectively to cardiac and pancreatic receptors.[119,151,170,205] Binding to cardiac receptors could mitigate the protective effects of ischemic conditioning; therefore, glyburide binding to sulfonylurea receptors on cardiac myocytes may result in increased infarct size and reduced left ventricular function following myocardial infarction.[107,108,125] In addition to differences in tissue selectivity, the risk of hypoglycemia varies among sulfonylureas.[109,110] Severe hypoglycemia can induce cardiac stress, which could precipitate QT prolongation and myocardial ischemia.[101,103] The risk of sulfonylurea-related hypoglycemia is highest with glyburide due to its longer duration of action and active metabolites.[109,110]

To further examine the possible causal relationship between sulfonylureas and adverse cardiovascular events, we were interested in examining the Bradford-Hill consideration of a dose-response relationship.[31] Although we have previously observed that higher daily doses of glyburide were associated with a higher risk of mortality among newly treated patients with type 2 diabetes, it is unclear if this dose-response relationship is specific to glyburide or extends to other sulfonylureas like gliclazide which is more pancreas-selective and has a lower risk of hypoglycmeia.[135] Indeed there appear to be important differences in the cardiovascular safety of these two sulfonylureas.[73,231] In addition, it is not clear if findings from our previous study would extend to an older population with different risk factors and different outcome measures.

Further, our previous study used cumulative exposure over the entire observation period, which might not accurately define exposure because the sulfonylurea dose may change over time to accommodate changes in glucose control or reduce the risk of hypoglycemia.

The objective of this study was to determine if there was a dose-response relationship between sulfonylureas and major adverse cardiovascular event risk. We hypothesized that exposure to higher doses of glyburide would be associated with a higher risk of adverse cardiovascular events compared to exposure to lower doses. Because gliclazide is likely more pancreas-selective and has a lower risk of hypoglycemia, we hypothesized there would be no significant difference in adverse cardiovascular event risk between higher and lower doses of gliclazide.

4.3. Methods

Population and setting

A population-based retrospective cohort study was conducted using administrative healthcare databases of Alberta Health (Alberta, Canada). Under provincially funded programs, all Alberta residents receive coverage for hospitalizations, emergency department visits, and physician services. Albertans aged ≥ 65 years also receive partial coverage (30% co-payment to a maximum of $25) for prescription medications. The administrative healthcare databases used to manage these programs are linkable and have been used extensively in previous epidemiologic studies because of the high level of accuracy and completeness of data.[207–211,231] In brief, the Discharge Abstract Database records information on hospital admissions; the Ambulatory Care database contains emergency department visits; the Practitioner Payments database captures office-based visits; the Alberta Vital Statistics database contains information on birth and death records; and the Population Registry file contains demographic information. The Alberta Blue Cross medication database captures dispensation claim information for individuals aged ≥ 65 years. The University of Alberta Health Research Ethics Board approved the study protocol (Appendix C).

Patients were eligible for inclusion in this study if they received a sulfonylurea dispensation between January 1998 and December 2010. New users were identified using a washout period of 365 days prior to the first sulfonylurea dispensation. During this period patients were allowed to receive any other antidiabetic drugs, but not a sulfonylurea drug. Only gliclazide and glyburide users were considered in this study as other sulfonylureas were rarely used (tolbutamide, n=15; chlorpropamide, n=24). If a patient received more than one sulfonylurea during the study period, follow-up was censored at the first dispensation record for the alternate sulfonylurea. This resulted in two separate sulfonylurea cohorts, a gliclazide cohort and a glyburide cohort.

Outcome measures

The main outcome was the occurrence of MACE, which included cardiovascular mortality, non-fatal acute coronary syndrome or non-fatal stroke.[232] If a patient experienced more than one component of this composite outcome, only the first event was considered.

Deaths were identified from the Alberta Vital Statistics database and non-fatal events were identified from the Discharge Abstract Database and Ambulatory Care database. A death or non-fatal event was considered attributable to a MACE if the primary diagnostic field or procedural code field contained an International Classification of Diseases (ICD-9/10) code of the respective outcome of interest (Appendix D). These codes have been used in other studies to identify MACE and have high positive predictive values (81 – 96%).[198,233]

Exposure level

In order to determine exposure level, we calculated an average daily dose for gliclazide or glyburide. We noticed that drug refill frequency was usually self-driven by the patient and any overlapping daily dose would erroneously inflate this value. In order to normalize patient drug exposure over follow up, we decided to update exposure level every 6-month interval. This was achieved by splitting each patient's follow up time into 6-month exposure windows and estimating the average daily dose of sulfonylurea received within each window. Figure 4-1 explains the algorithm used to calculate the average daily dose. As

done previously, we identified a median daily dose for gliclazide and glyburide and assigned each window to the low- or high-dose group if the average daily dose in that window was below or above the median, respectively.[135]

We made a number of assumptions to calculate the average daily dose for each drug refill. First, we assumed that the supply from each refill was consumed before the start of the next refill. Second, we assumed drug refill interval (duration between two consecutive refills) for the last dispensation would be equivalent to the patient's average refill interval between previous dispensations. Although the days supplied information would better reflect the duration of a dispensation, this field was introduced in the Alberta Blue Cross database in 2004 and therefore not available for a large proportion of dispensations. For patients with a single sulfonylurea dispensation during follow up, their refill interval was assumed to equal the population's average refill interval. Third, as there were two formulations available for gliclazide, we assumed the 80 mg immediate release formulation to be equivalent to the 30 mg modified release formulation, as indicated in the product monograph.[234]

Covariates

The baseline period to capture information on covariates was 3 years prior to cohort entry date, which was defined at the first sulfonylurea refill. Information on baseline demographic characteristics (age and sex) was collected from the Population Registry database. Cohort entry year was identified to control for potential differences in temporal trends of gliclazide and glyburide use over the observation period. Concurrent antidiabetic drugs (including metformin, thiazolidinediones [TZDs], acarbose, and insulin); cardiovascular therapies (including antihypertensive drugs, lipid lowering drugs, antiplatelet drugs, oral anticoagulants, digoxin, nitrates and anti-arrhythmia drugs) as well as hormone replacement therapies and cyclo-oxygenase-2 (COX-2) inhibitors were identified from dispensation records. Information on comorbidities were captured from the Discharge Abstract Database, the Ambulatory Care database, and the Practitioner Payments database using ICD 9/10 codes as suggested in the Elixhauser Index.[212,235] This list was supplemented by including ICD 9/10 codes for ischemic heart disease, cerebrovascular disease, hyperlipidemia and hypoglycemia (Appendix D).

As a high exposure level may indicate more severe disease, we used proxies for diabetes severity, including duration of diabetes (calculated as the time between start of any antidiabetic therapy and the start of sulfonylurea therapy), the presence of diabetes complications (neuropathy, retinopathy and nephropathy) and the number of antidiabetic drugs. As intensity of healthcare utilization might also indicate disease severity, we identified the number of hospital admissions, physician visits and distinct prescription drugs during the baseline period.[236,237] These proxy measures were used to control for confounding by disease severity.

To control for selection bias due to possible differences in management, physician service codes for guideline concordant procedures, which included retinopathy screening, lipid, blood glucose, or renal function assessment, as well as mammography, prostate hypertrophy, and bone mineral densitometry screening were captured.[54]

Propensity score models

A propensity score model was developed to calculate the patient-specific probability of initiating low- or high-dose sulfonylurea. Using a logistic regression model, the dependent variable was exposure level at baseline (within the first 6-month window) and the independent variables were all baseline covariates listed previously.[238,239] We chose this approach for calculating a propensity score because a preliminary analysis of our data determined that 72% of patients started and ended follow up in the same exposure group (Table 4-1). Propensity scores were then divided into quintiles and used as a covariate in the final analysis models (Table 4-2; Figure 4-2). The model yielded a c-statistic of 0.59.

Statistical analyses

Descriptive statistics were calculated for baseline characteristics, stratified by gliclazide or glyburide. To determine the risk of MACE, patients were followed from the date of first gliclazide or glyburide refill until they had the outcome of interest or were censored. Patients were censored if they died, switched to a different sulfonylurea, discontinued the sulfonylurea (expiry of last refill interval), left the province, or the observation period ended (December 31, 2010). Unadjusted incidence rates for MACE were calculated for each drug,

stratified by exposure level. Cox proportional hazards regression models were used to estimate the HR and 95% CI for MACE comparing low (reference) and high doses for gliclazide and glyburide, separately. All models were adjusted for propensity scores quintiles.

We found no evidence for violation of the proportional hazard assumption as assessed by the scaled Schoenfeld residuals tests. All analyses were conducted using Stata12.0 (StataCorp. 2011. *Stata Statistical Software: Release 12*. College Station, TX: StataCorp LP).

Secondary analysis

We were also interested in comparing the risk of MACE between gliclazide and glyburide within each exposure level. A separate propensity score model was constructed where the dependent variable was baseline exposure to gliclazide or glyburide and the independent variables were baseline covariates (c-statistic = 0.67). Hazard ratios (95% CI) for MACE were estimated to compare gliclazide (reference) and glyburide within low- and high-dose groups using Cox proportional hazards regression models while adjusting for propensity score quintiles.

Sensitivity analyses

To assess robustness of our observations, we repeated the analyses with three different initial assumptions. First, we shortened each exposure window into 3-month intervals. Second, we used the last observation carried forward method to estimate the refill interval for the last dispensation. Third, instead of using median split to define exposure levels, each exposure window was assigned to the low- or high-dose group if the average daily dose was below or above the World Health Organization defined daily dose (DDD) for gliclazide (DDD = 60 mg) or glyburide (DDD = 10 mg), respectively. In addition, we restricted the analysis to patients who were MACE-free at baseline.

4.4. Results

Baseline characteristics

Out of 125,565 patients with antidiabetic drug dispensations, we identified 8,918 new users of gliclazide and 7,483 new users of glyburide (Figure 4-3). The mean (SD) age was 74.8 (6.6) years, 8,917 (54.4%) were males and the mean (SD) duration of follow up was 2.6 (2.8) years. Table 4-3 summarizes baseline characteristics for gliclazide and glyburide users according to their exposure level during the first 6-month window. In general, the low-dose group was older, had fewer women, higher prevalence of concurrent drug use, but similar prevalence of comorbid conditions compared to the high-dose group for both drugs.

Gliclazide users had 51,394 exposure windows with a total follow up duration of 23,342 person-years. Glyburide users had 41,468 exposure windows and 18,760 person-years of follow up. The median daily dose was 48.0 mg for gliclazide and 6.5 mg for glyburide.

Primary analysis

The primary outcome occurred in 1,584 (9.7%) patients during the follow up period (37.2 events per 1,000 PY; Figure 4-4). Among gliclazide users, incidence rates for MACE were 34.0 per 1,000 PY for the low-dose group and 36.5 per 1,000 PY for the high-dose group. After adjusting for propensity scores, the gliclazide dose groups were associated with a similar risk for MACE (adjusted HR 1.14; 95% CI 0.99–1.30, p=0.07).

For glyburide users, the low-dose group had an incidence rate for MACE of 38.2 per 1000 PY; while, the high-dose group had an incidence rate of 43.1 per 1000 PY (Figure 4-4). Adjusting for propensity scores revealed a significantly higher risk for MACE associated with the high-dose group of glyburide (adjusted HR 1.18; 95% CI 1.02–1.36, p=0.02) compared to the low-dose group.

Secondary analysis

Gliclazide and glyburide were directly compared within each exposure level (Figure 4-4). Among the low-dose group, there was no significant difference in the risk for MACE between gliclazide and glyburide users (adjusted HR 1.14; 95% CI 0.99–1.32, p=0.08). Among the high-dose group, however, glyburide users had a higher risk of MACE (adjusted HR 1.21; 95% CI 1.05–1.39, p<0.01) compared to gliclazide users.

Sensitivity analyses

Shortening the exposure window into 3-month intervals, using the last observation carried forward to estimate the last refill interval, using the defined daily dose to assign windows to low- and high-dose groups and restricting the analysis to MACE-free patients did not make substantive changes to the magnitude or direction of our primary analysis (Table 4-4).

4.5. Discussion

Among this group of elderly patients with type 2 diabetes who newly started sulfonylureas, there appears to be a dose-response relationship between glyburide and the risk of MACE. In contrast, the risk of MACE was similar between dose groups of gliclazide. When glyburide and gliclazide were compared directly, high-dose of glyburide was associated with a higher risk of MACE relative to high-dose of gliclazide. However, the risk was similar for both drugs when compared within the low-dose group. These observations add to existing evidence suggesting that sulfonylureas vary with respect to their cardiovascular risk profile, especially when used at higher doses.[198,231]

Concerns about the cardiovascular safety of sulfonylureas date back to publication of the University Group Diabetes Program (UGDP) in 1970.[49] Twenty-eight years later, a larger randomized controlled trial, the United Kingdom Prospective Diabetes Study (UKPDS), was published but suggested no association between sulfonylurea use and adverse cardiovascular outcomes.[64] Other clinical trials with sulfonylureas had small sample sizes, short follow-up periods, and were not designed to evaluate effects on cardiovascular

outcomes.[50] More recent diabetes trials have focused on evaluating the effect of intensive glycemic control rather than the effect of individual drugs.[86–88] Therefore, most of the evidence about the cardiovascular safety of sulfonylureas comes from observational studies, unfortunately with mixed results.[50] When data from 18 randomized controlled trials and observational studies were pooled in a network meta-analysis, gliclazide was associated with a significantly lower risk of mortality compared to glyburide (Relative Risk 0.65; 95% CI 0.53–0.79).[73]

In the current study, we assessed the dose-response relationship between sulfonylureas and adverse cardiovascular events; a consideration proposed by Sir Austin Bradford Hill when evaluating causality from observational data.[31] Other considerations, like biological plausibility, temporality, and coherence between human and animal studies, are well-supported in the literature.[50] Although the magnitude of effect and consistency of results are somewhat weak,[198,231] current ongoing clinical trials might help to provide stronger evidence to evaluate the cardiovascular safety of sulfonylureas.[84,85] Evidence of a dose-response relationship between sulfonylureas and adverse cardiovascular outcomes, however, is limited to two observational studies. The first study showed a higher mortality risk associated with higher doses compared to lower doses of glyburide (HR 1.29; $p<0.05$).[135] The second study categorized sulfonylureas as one group and found that higher doses of sulfonylureas were associated with a higher risk for heart failure compared to lower doses (HR 1.38; 95% CI 1.20–1.60).[240] Our study confirms previous observations of a dose-response relationship between glyburide and adverse cardiovascular events. These harmful effects may be explained by the effects of glyburide on ischemic conditioning, its risk of hypoglycemia or by other less-established mechanisms such as increased plasma proinsulin:insulin or weight gain.[76,110,119,205] Our study also improves on the previous studies by using a more refined definition of exposure and extends the observation to other sulfonylureas, like gliclazide. This particular sulfonylurea is believed to be more pancreas-selective, has a lower risk of hypoglycemia than other sulfonylureas, and was suggested to show some anti-oxidant and anti-platelet properties.[110,119,205,226,228] We did not observe a dose-response relationship between gliclazide and MACE.

Similar to other observational studies, there are several important limitations inherent to the design of this study that limits our conclusion to an association rather than a causal relationship. First, a missing dose-response relationship among gliclazide users does not exclude an increased risk of MACE in this group. It is possible that the adverse cardiovascular effects of gliclazide develop at very low doses, without further increase in risk at higher doses. Second, our databases lacked data on important confounding factors, such as smoking status, blood pressure, blood glucose, and cholesterol levels. However, we used an extensive list of drugs and diagnostic codes to identify comorbidities, including hypertension and dyslipidemia and included these in the adjusted analyses. Third, despite adjusting for proxies of diabetes severity, guideline concordant procedures, as well as propensity scores, selection bias remains probable. Fourth, we used dispensation records as a proxy for actual drug consumption, which might overestimate exposure. Fifth, there have been temporal changes in the use of glyburide and gliclazide over the observation period, which might indicate changes in glycemic targets and cardiovascular management guidelines. We accounted for these temporal changes by including cohort entry year in the adjusted analyses. Sixth, the generalizability of our findings is limited to elderly patients with type 2 diabetes. Last, we used ICD codes to identify comorbidities and outcomes from administrative health records. Although there is potential for misclassification, we believe this is acceptable given the high positive predictive values for most of these codes (81 – 96%).[212,214,233]

Conclusions

Among this group of elderly patients with type 2 diabetes who newly started a sulfonylurea, there appears to be important differences in the dose-response relationship among sulfonylureas. These observations provide additional evidence that gliclazide may have a better cardiovascular safety profile than glyburide. Due to the observational nature of the study; however, these findings require confirmation in an appropriately designed controlled clinical trial.

Table 4-1. Comparison of dose groups between first and last exposure windows in patients with at least 2 exposure windows

A. Gliclazide users

	Last exposure window		
First exposure window	***Low***	***High***	***Total***
Low	2,397	1,319	3,716
High	449	2,173	2,622
Total	2,846	3,492	6,338

B. Glyburide users

	Last exposure window		
First exposure window	***Low***	***High***	***Total***
Low	1,743	1,061	2,804
High	310	1,739	2,049
Total	2,053	2,800	4,853

Table 4-2. Logistic regression model for the probability of receiving high dose group compared to low dose group

Covariate	*Odds ratio*	*P>|z|*	*95% confidence interval*
Drug			
Gliclazide*	1		
Glyburide	1.103	0.003	(1.033 - 1.177)
Age	0.974	0.001	(0.969 - 0.979)
Sex			
Female*	1		
Male	1.069	0.063	(0.996 - 1.146)
Cohort entry year			
1999-2002*	1		
2003-2006	1.109	0.011	(1.024 - 1.200)
2007-2010	1.104	0.032	(1.009 - 1.208)
Diabetes severity			
Diabetes duration	0.971	0.014	(0.949 - 0.994)
Number of diabetes complications			
0*	1		
1	1.013	0.801	(0.917 - 1.119)
>1	0.95	0.709	(0.724 - 1.246)
Number of antidiabetic drugs			
1*	1		
2	0.888	0.397	(0.674 - 1.170)
>2	0.514	0.131	(0.217 - 1.219)
No. of hospital admissions	1.008	0.074	(0.999 - 1.017
No. of physician visits	0.998	0.011	(0.997 - 0.999)
No. of distinct prescription drugs	1.005	0.001	(0.999 - 1.012)
Guideline concordant procedures^	0.98	0.541	(0.917 - 1.047)
Concurrent drugs			
Metformin	1.08	0.06	(0.997 - 1.171)
Thiazolidinediones	1.383	0.012	(1.073 - 1.784)
Acarbose	1.765	0.065	(0.964 - 3.232)
Insulin	1.492	0.014	(1.084 - 2.052)
ACE inhibitors or ARBs	0.841	<0.001	(0.778 - 0.909)
Beta-blockers	0.908	0.021	(0.837 - 0.985)
Diuretics	1.02	0.608	(0.945 - 1.101)
Calcium channel blockers	0.969	0.419	(0.897 - 1.046)
Other antihypertensive agents	0.817	0.054	(0.666 - 1.004)
Digoxin	1.287	<0.001	(1.128 - 1.468)
Anti- arrhythmia	1.236	0.075	(0.979 - 1.560)
Lipid lowering agents	0.808	<0.001	(0.747 - 0.875)
Nitrate	0.999	0.978	(0.899 - 1.109)
Antiplatelets	1.205	0.029	(1.019 - 1.425)

Anticoagulants	0.923	0.198	(0.817 - 1.043)
Hormone replacement therapy	0.959	0.519	(0.843 - 1.090)
COX-2 inhibitors	0.977	0.588	(0.899 - 1.062)
Comorbidities			
Ischemic heart disease	1.033	0.469	(0.947 - 1.126)
Congestive heart failure	1.083	0.136	(0.975 - 1.202)
Cardiac arrhythmia	0.928	0.164	(0.834 - 1.031)
Valvular disease	1.059	0.482	(0.902 - 1.245)
Pulmonary circulation disorders	0.951	0.596	(0.790 - 1.145)
Peripheral vascular disease	1.106	0.117	(0.975 - 1.253)
Hypertension, uncomplicated	1.059	0.156	(0.978 - 1.147)
Hypertension, complicated	1.006	0.943	(0.843 - 1.202)
Paralysis	0.825	0.210	(0.611 - 1.115)
Other neurological disorders	1.125	0.209	(0.936 - 1.352)
Chronic pulmonary disease	0.999	0.971	(0.925 - 1.078)
Hypothyroidism	0.965	0.516	(0.867 - 1.074)
Renal failure	0.945	0.459	(0.815 - 1.097)
Liver disease	1.008	0.945	(0.798 - 1.274)
Peptic ulcer disease	1.152	0.269	(0.896 - 1.481)
HIV/AIDS	1.935	0.641	(0.120 - 31.093)
Lymphoma	1.074	0.646	(0.792 - 1.455)
Metastatic cancer	0.949	0.646	(0.760 - 1.186)
Solid tumor without metastasis	0.967	0.530	(0.871 - 1.073)
Rheumatoid arthritis/collagen vascular diseases	0.915	0.164	(0.807 - 1.037)
Coagulopathy	0.991	0.931	(0.817 - 1.203)
Obesity	1.306	0.001	(1.121 - 1.522)
Weight loss	0.946	0.634	(0.753 - 1.189)
Fluid and electrolyte disorders	1.032	0.535	(0.934 - 1.141)
Blood loss anemia	1.017	0.933	(0.691 - 1.495)
Drug abuse	0.936	0.439	(0.791 - 1.107)
Alcohol abuse	0.95	0.668	(0.750 - 1.203)
Drug abuse	0.991	0.959	(0.711 - 1.382)
Psychoses	0.976	0.825	(0.787 - 1.210)
Depression	0.983	0.715	(0.899 - 1.076)
Acute hypoglycemia, treated in emergency room	1.149	0.301	(0.883 - 1.495)
Cerebrovascular disease	0.931	0.234	(0.828 - 1.047)
Hyperlipidemia	1.04	0.433	(0.943 - 1.148)

* Baseline category
^ Guideline concordant procedures included screening for any of the following: (lipid profile, blood glucose, renal function, eye exam, mammography, prostate hypertrophy and bone density scan)
ACE: angiotensin-converting-enzyme inhibitor, ARB: angiotensin II receptor antagonist

Table 4-3. Baseline characteristics by exposure level

Characteristic	Gliclazide (n=8,918)			Glyburide (n=7,483)		
	Low (n=5,183)	*High (n=3,735)*	*p-value*	*Low (n=4,083)*	*High (n=3,400)*	*p-value*
Age, mean (SD), years	75.7 (6.5)	74.6 (6.6)	<0.01	74.9 (6.5)	73.7 (6.4)	<0.01
Men, n (%)	2,778 (53.6)	2,113 (56.6)	<0.01	2,134 (52.3)	1,892 (55.6)	<0.01
Cohort entry by year, n (%)						
1999 - 2002	1,595 (30.8)	1,218 (32.6)	<0.01	2,219 (54.3)	1,771 (52.1)	0.02
2003 - 2006	1,435 (27.7)	1,098 (29.4)		1,207 (29.6)	1,003 (29.5)	
2007 - 2010	2,153 (41.5)	1,419 (38.0)		657 (16.1)	626 (18.4)	
Duration of follow up, mean (SD), years	2.62 (2.84)	2.61 (2.82)	0.84	2.69 (2.86)	2.29 (2.72)	<0.01
Duration of diabetes, mean (SD), years	1.23 (2.11)	1.06 (1.93)	<0.01	0.57 (1.39)	0.46 (1.26)	<0.01
Antidiabetic drugs, n (%)						
Metformin	2,506 (48.4)	1,789 (47.9)	0.67	1,359 (33.3)	1,044 (30.7)	0.02
Thiazolidinediones	435 (8.4)	330 (8.8)	0.46	162 (4.0)	160 (4.7)	0.12
Acarbose	14 (0.3)	10 (0.3)	0.98	9 (0.2)	16 (0.5)	0.06
Insulin	61 (1.2)	64 (1.7)	0.03	43 (1.1)	48 (1.4)	0.16
Other drugs, n (%)						
ACE inhibitors or ARBs	3,168 (61.1)	2,101 (56.3)	<0.01	1,986 (48.6)	1,444 (42.5)	<0.01
Beta-blockers	1,645 (31.7)	1,041 (27.9)	<0.01	1,016 (24.9)	763 (22.4)	0.01
Calcium channel blockers	1,594 (30.8)	1,059 (28.4)	0.01	1,107 (27.1)	811 (23.9)	<0.01
Diuretics	2,330 (45.0)	1,627 (43.6)	0.19	1,667 (40.8)	1,238 (36.4)	<0.01
Other antihypertensive drugs	145 (2.8)	77 (2.1)	0.03	119 (2.9)	78 (2.3)	0.1
Nitrates	881 (17.0)	575 (15.4)	0.04	602 (14.7)	464 (13.6)	0.18
Digoxin	454 (8.8)	356 (9.5)	0.21	359 (8.8)	315 (9.3)	0.48
Anticoagulant drugs	688 (13.3)	443 (11.9)	0.05	435 (10.7)	343 (10.1)	0.42
Lipid Lowering drugs	2,389 (46.1)	1,498 (40.1)	<0.01	1,293 (31.7)	932 (27.4)	<0.01

Comorbid conditions, n (%)						
Hypertension	3,882 (74.9)	2,721 (72.9)	0.03	2,798 (68.5)	2,262 (66.5)	0.07
Ischemic heart disease	1,586 (30.6)	1,135 (30.4)	0.83	1,181 (28.9)	945 (27.8)	0.28
Congestive heart failure	928 (17.9)	665 (17.8)	0.90	657 (16.1)	555 (16.3)	0.79
Cardiac arrhythmia	928 (17.9)	623 (16.7)	0.13	678 (16.6)	527 (15.5)	0.20
Cerebrovascular disease	518 (10.0)	361 (9.7)	0.61	430 (10.5)	297 (8.7)	<0.01
Peripheral vascular disease	384 (7.4)	289 (7.7)	0.56	285 (7.0)	254 (7.5)	0.41
Dyslipidemia	801 (15.5)	574 (15.4)	0.91	530 (13.0)	424 (12.5)	0.51
Hypoglycemia	24 (0.5)	18 (0.5)	0.90	30 (0.7)	45 (1.3)	0.01
Measures of disease burden, median (IQR)						
Number of Elixahuser's comorbid conditions	2 (1-4)	2 (1-4)	0.69	2 (1-4)	2 (1-4)	0.01
Number of hospital admissions	1 (0-3)	1 (0-3)	0.07	1 (0-2)	1 (0-2)	0.23
Number of physician visits	41 (26-61)	39 (23-60)	<0.01	38 (23-58)	36 (20-58)	<0.01
Number of distinct prescription drugs	12 (7-18)	11 (7-17)	<0.01	10 (6-16)	9 (5-15)	<0.01

* P<0.05

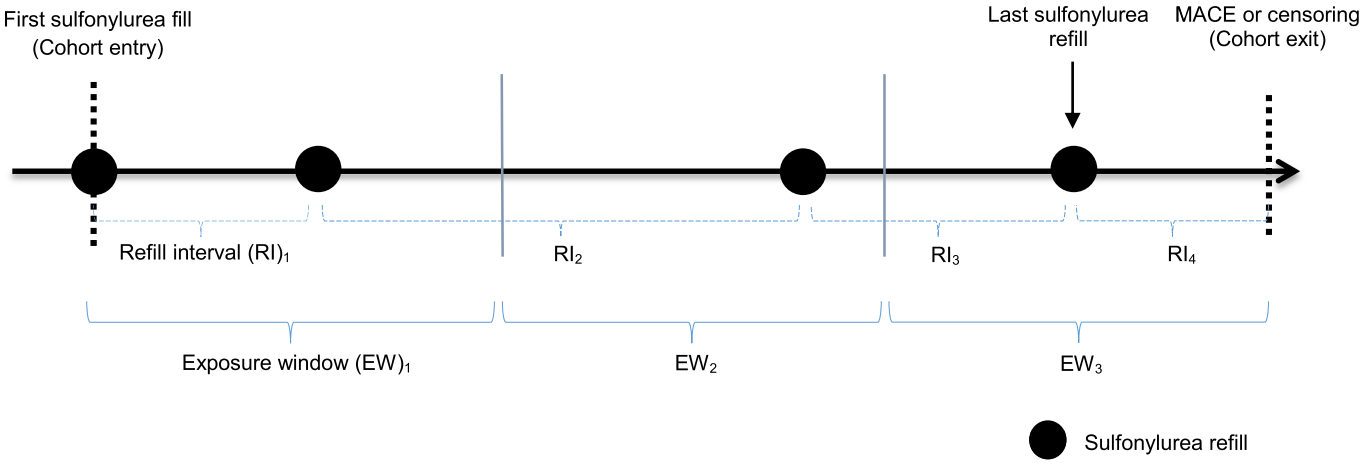
ACE: angiotensin-converting-enzyme inhibitor, ARB: angiotensin II receptor antagonist, IQR: interquartile range, SD: standard deviation

Table 4-4. Sensitivity analyses hazard ratio of major adverse cardiovascular events for glyburide and gliclazide users

	Events no. (events/1000 PY)		*Crude HR (95% CI)*	*Adjusted HR (95% CI)*
	Low (REF)	*High*		
Exposure window = 3-month				
Gliclazide	390 (33.3)	432 (37.1)	1.13 (0.99 – 1.30)	1.17 (1.02 – 1.34)
Glyburide	351 (37.2)	411 (44.1)	1.19 (1.03 – 1.38)	1.24 (1.07 – 1.43)
Last refill interval = last observation carried forward				
Gliclazide	407 (34.7)	406 (35.0)	1.03 (0.90 – 1.18)	1.07 (0.93 – 1.22)
Glyburide	350 (37.0)	396 (42.7)	1.17 (1.02 – 1.36)	1.22 (1.05 – 1.41)
Exposure level categorized by defined daily dose				
Gliclazide	543 (34.4)	279 (37.0)	1.08 (0.94 – 1.25)	1.11 (0.96 – 1.28)
Glyburide	503 (39.0)	259 (44.1)	1.14 (0.98 – 1.33)	1.19 (1.02 – 1.38)
Restricted to MACE-free patients				
Gliclazide	303 (29.1)	335 (32.3)	1.11 (0.95 – 1.30)	1.15 (0.98 – 1.34)
Glyburide	281 (33.0)	323 (38.5)	1.17 (0.99 – 1.37)	1.20 (1.02 – 1.42)

CI: confidence interval; HR: Hazard ratio; MACE: major adverse cardiovascular events, PY: person-year

Figure 4-1. Diagram explaining the estimation of exposure level



In order to assess exposure during each 6-month exposure window, we followed the steps below:

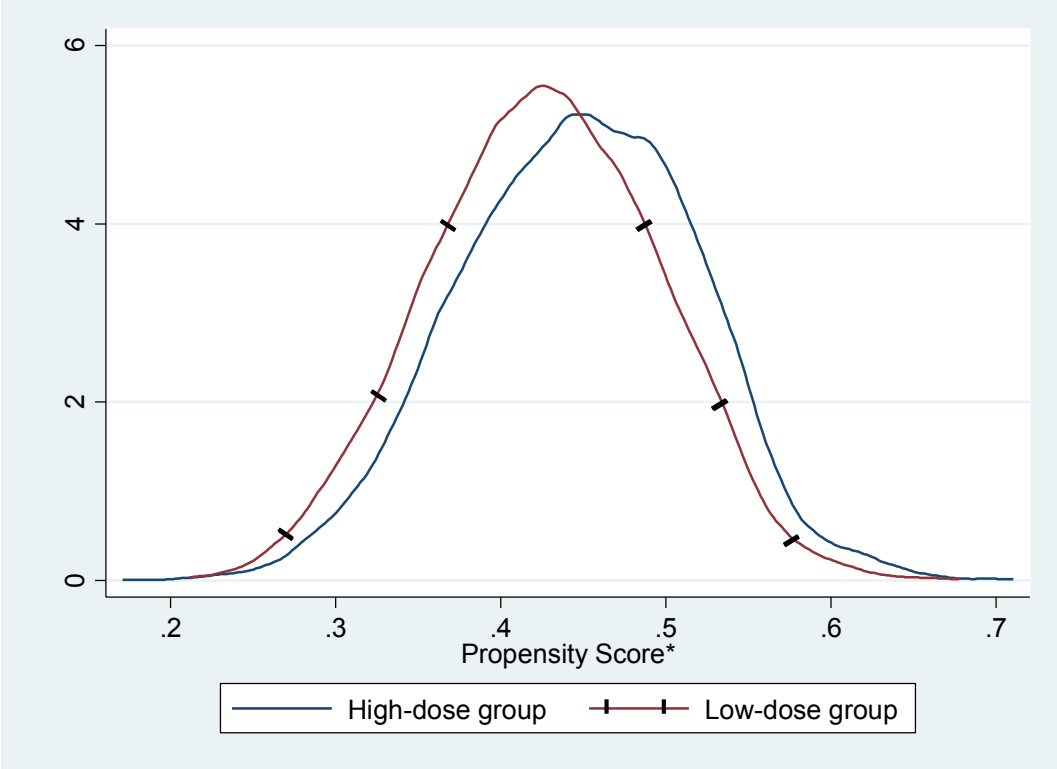
1- For each drug refill, we collected information on refill date, number of tablets filled, tablet strength and the time to next drug refill (RI)
2- We then calculated the average daily dose provided by each refill using the following formula:

$$\frac{number\ of\ tablets\ filled\ x\ tablet\ strength}{refill\ interval}$$

3- For each exposure window (EW), we aggregated the daily doses from all refills within window and calculated the window daily dose as:

$$\frac{\sum(daily\ doses\ from\ all\ refills\ within\ window)}{window\ duration}$$

Figure 4-2: Distribution of propensity scores by exposure level



*Probability of receiving high-dose group

Figure 4-3. Patient flow diagram

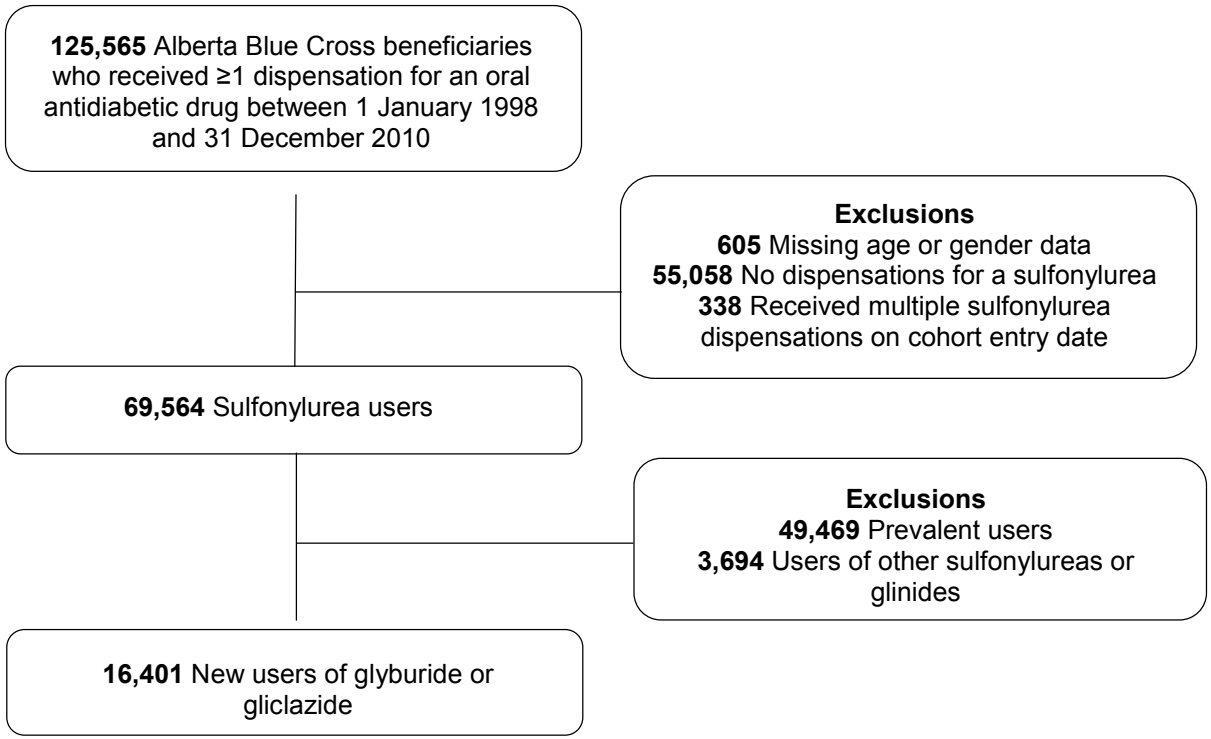
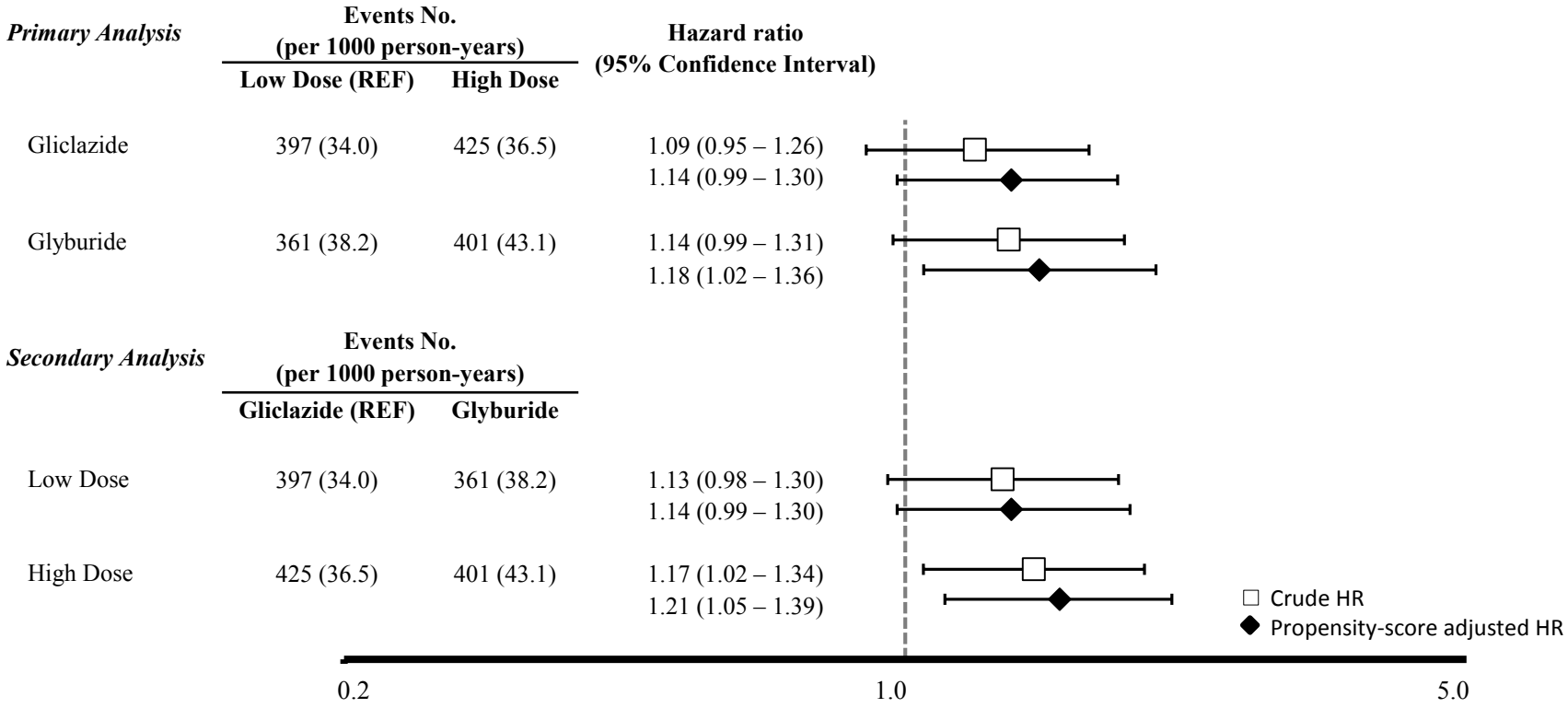


Figure 4-4. Hazard ratio of major adverse cardiovascular events for glyburide and gliclazide users



CHAPTER 5

Sulfonylurea Use is Associated with Larger Infarct Size in Patients with Diabetes and ST-Elevation Myocardial Infarction[4]

5.1. Abstract

Background

Animal models have demonstrated that sulfonylureas increase the size of myocardial infarction; however, data in humans is scarce. This study evaluated the association between sulfonylurea use and infarct size in diabetes patients with ST-elevation myocardial infarction (STEMI).

Methods

Consecutive STEMI patients admitted in Edmonton, Canada between 2006 and 2011 were enrolled in a regional prospective registry program. Patients with type 2 diabetes were identified from this group and the maximum recorded troponin I (max cTnI) within the first 48 hours of chest pain onset was used as the primary outcome to quantify infarct size. The relationship between preadmission sulfonylurea use and max cTnI was assessed using multivariable linear regression to adjust for patient demographics, cardiovascular risk factors, clinical data on admission, ischemia time, reperfusion therapy, and preadmission drugs.

Results

[4] A version of this chapter has been accepted for publication as Abdelmoneim AS, Welsh R, Eurich DT, Simpson SH. Sulfonylurea use is associated with larger infarct size in patients with diabetes and ST-elevation myocardial infarction. Int J Cardiol. 2016;202:126-130.

There were 560 STEMI patients with type 2 diabetes; mean (standard deviation; SD) age was 63.3 (12.8) years, 395 (70.5%) were male, 216 (38.6%) received primary percutaneous intervention, and 211 (37.7%) received fibrinolysis. The max cTnI was higher in 146 sulfonylurea users compared to 414 non-sulfonylurea users (mean (SD): 49.8 (74.3) ng/mL versus 39.9 (50.4) ng/mL, respectively; adjusted between-group difference: 12.9 ng/mL; 95% confidence interval [CI] 0.3–25.5; p=0.044).

Conclusion

This study adds further evidence to the proposed causal relationship between sulfonylureas and adverse cardiovascular events by observing a significant difference in infarct size among type 2 diabetes patients presenting with STEMI. Clinicians should consider this association when prescribing sulfonylureas to manage patients with type 2 diabetes.

5.2. Introduction

Type 2 diabetes mellitus is a serious metabolic condition with devastating cardiovascular complications.[43,241] It is estimated that patients with type 2 diabetes have a 2- to 3-fold higher risk of major cardiovascular disease compared to those without diabetes.[39] This higher risk is important because cardiovascular-related deaths account for approximately one half of all deaths in patients with type 2 diabetes.[242]

In addition to the higher cardiovascular risk conferred by diabetes itself, some drugs used to treat this chronic disease also increase the risk of adverse cardiovascular events.[61] Perhaps the most widely-known example is the association between rosiglitazone and myocardial infarction risk.[45,46] The cardiovascular safety of sulfonylureas has also been widely debated since the UGDP trial reported a significantly higher rate of cardiovascular deaths among patients using tolbutamide compared to placebo.[49] However, more recent trials failed to replicate the UGDP findings. For example, in the UKPDS patients receiving sulfonylureas in the intensive treatment arm had a similar cardiovascular risk to patients in the conventional treatment arm.[64] Inconsistent observations and conflicting findings from more recent observational studies have fueled the controversy regarding the possible causal relationship between sulfonylureas and adverse cardiovascular events.[50] Two ongoing randomized controlled trials are comparing the risk of cardiovascular outcomes between sulfonylureas and either linagliptin (CAROLINA) or pioglitazone (TOSCA-IT).[84,243] Although these studies may provide some insight into the relative cardiovascular safety of sulfonylureas, results are not expected until 2018.

Two biologically plausible mechanisms have been suggested to explain the potential cardiovascular effects of sulfonylureas. The first mechanism is related to sulfonylurea-induced hypoglycemia, which may trigger QT prolongation and myocardial infarction.[101,105] In the second mechanism, sulfonylureas are believed to abolish the protective effects of ischemic conditioning, leading to increased infarct size and reduced left ventricular function.[106,151] Interestingly, the risk of hypoglycemia and the ability to abolish ischemic conditioning seem to differ between individual sulfonylureas. [108–

[110,119,205] Although these harmful effects were demonstrated in several diabetic animal models,[125,244] there is limited, and inconclusive information about the effect of sulfonylureas on myocardial infarct size in humans.[70,145,245]

With these issues in mind, the objective of this study was twofold. First, to evaluate the association between preadmission sulfonylurea use and infarct size in a group of type 2 diabetes patients presenting with STEMI using a regional Canadian STEMI registry. Second, as individual sulfonylureas might show different pharmacologic properties, we compared infarct size between individual sulfonylureas.

5.3. Methods

Study design, setting and patients

We conducted a cohort study using patient information from a regional Canadian STEMI registry, the VHR registry.[246] Briefly, the Vital Heart Response (VHR) was a prospective registry of all STEMI patients admitted to hospitals within Edmonton, Canada between October 2006 and October 2011. This registry was initially developed as a quality improvement project to evaluate management and outcomes of STEMI patients. Patients were enrolled in the registry if an ECG showed a new ST-elevation in at least 2 contiguous leads. Once an eligible patient was identified, trained data abstractors prospectively collected information on patient demographics, cardiovascular risk factors, clinical data on admission, ischemia time, reperfusion therapy, cardiovascular drugs used prior to admission, cardiac assessments (including enzymes, electrocardiograms, and echocardiograms), and in-hospital events.

The study reported here was approved by the University of Alberta Ethics Board (Appendix C). Patients in the VHR registry were eligible for inclusion if diabetes was listed in their medical history. We used the patient's unique health care number and discharge date to locate the relevant chart and supplemented the VHR registry data with information on diabetes management. We identified the type of diabetes (type 1, type 2, or pre-diabetes), antidiabetic drugs used prior to admission, and diabetes-related laboratory data. Patients were subsequently excluded from the analysis if they had type 1 diabetes, pre-

diabetes, or the diabetes status was not specified in the chart. In the event a patient appeared in the VHR registry multiple times because they were admitted for multiple STEMI events during our observation period, only the first admission was considered.

Exposure group

We assigned patients to the sulfonylurea group if there was information documented in the chart indicating the patient was using glyburide, gliclazide, or any other sulfonylurea prior to admission. We assumed the patient was not using a sulfonylurea prior to admission if there was no information about sulfonylurea use in the chart.

As we were also interested in comparing the effect of individual sulfonylureas on infarct size, the sulfonylurea users were further stratified according to their use of either gliclazide or glyburide prior to STEMI admission. One patient was excluded from this subgroup analysis because they were using glimepiride prior to STEMI admission.

Outcome measures

The primary outcome variable was the maximum recorded troponin I (max cTnI) within the first 48 hours of chest pain onset. This outcome measure was chosen to quantify infarct size for a number of reasons. First, troponin I was regularly measured in patients presenting with cardiac chest pain. Second, it is more specific to the heart than other biomarkers, such as creatine kinase.[247] Third, it has a good correlation (r=0.61 to 0.91) with gold standard measures of myocardial infarction size, such as magnetic resonance imaging (MRI) and single-photon emission computed tomography (SPECT).[248–251] Fourth, it has been used in previous studies to evaluate the effect of drugs on myocardial infarct size.[252–254]

As secondary outcomes, we identified the maximum recorded total creatine kinase (max CK) within the first 48 hours of chest pain onset and a composite outcome variable of in-hospital sequelae, which included heart failure, cardiogenic shock, cardiac arrest, and death. Information on all outcome data were obtained from the VHR registry.

Covariates

The VHR registry provided each patient's age, sex, body mass index (BMI), cardiovascular risk factors (hypertension, hypercholesterolemia, angina, previous myocardial infarction and coronary reperfusion, and smoking status), clinical data on admission (heart rate, blood pressure, blood glucose, serum creatinine and total cholesterol), ischemia time (time from chest pain onset to reperfusion), and reperfusion therapy (percutaneous coronary intervention or thrombolysis). The VHR registry and our own review of the patient charts identified preadmission use of all cardiovascular (antihypertension, antiplatelet, anticoagulants, nitrates and lipid lowering), antidiabetic drugs, and additional clinical data (blood glucose, cholesterol level and serum creatinine).

Statistical analysis

Baseline characteristics were described according to preadmission sulfonylurea use. Continuous data were presented as mean and SD and categorical data were presented as frequency and percentage. Student's t-test and chi-square test were used to compare baseline differences between the two exposure groups for continuous and categorical data, respectively.

The max cTnI within the first 48 hours of chest pain onset was identified and compared between non-sulfonylurea (reference group) and sulfonylurea users and between gliclazide (reference group) and glyburide users by Student's t-test. In order to control for potential confounding factors between groups, a multivariable linear regression model was used to assess the relationship between sulfonylurea use and max cTnI. Similar methods were used to compare max CK between groups; while a multivariable logistic regression model was used to estimate the odds ratio (OR) and 95% confidence interval (CI) of in-hospital composite events between non-sulfonylurea and sulfonylurea users and between gliclazide and glyburide users. All models were adjusted for patient demographics, cardiovascular risk factors, clinical data on admission, ischemia time, reperfusion therapy, and preadmission drugs.

To maximize the use of all available data and to minimize the bias potentially generated by excluding incomplete data, we imputed missing data for BMI, heart rate, blood pressure, blood glucose, serum creatinine and total

cholesterol using multiple imputation with 5 iterations.[255] For all analyses, *p*-values ≤ 0.05 were considered to indicate statistical significance. All analyses were performed using Stata 12.0 (StataCorp. LP, College Station, TX, USA).

5.4. Results

Demographics

A total of 560 patients with STEMI and type 2 diabetes met the study inclusion criteria (Figure 5-1). The mean (SD) age for this group was 63.3 (12.8) years, 395 (70.5%) were men, 216 (38.6%) received primary percutaneous intervention, and 211 (37.7%) received fibrinolysis (Table 5-1). Clinical data were missing in <10% of patients, with the exception of cholesterol levels, which were missing in approximately 20% of patients. According to preadmission antidiabetic drug use, 414 patients received no sulfonylurea and 146 patients received a sulfonylurea. Sulfonylurea users were older, and more likely to have used metformin, thiazolidinediones (TZDs), angiotensin-converting-enzyme inhibitors and antiplatelet agents prior to admission, but less likely to have used insulin. Both groups were similar in terms of sex, cardiovascular risk factors, clinical data on admission, and reperfusion management.

Sulfonylurea vs. no sulfonylurea

Sulfonylurea users had higher max cTnI compared to non-sulfonylurea users (mean [SD]: 49.8 [74.3] ng/mL versus 39.9 [50.4] ng/mL, respectively; p=0.085) (Table 5-2). After adjusting for baseline covariates and reperfusion management, the max cTnI was significantly higher among sulfonylurea users compared to non-sulfonylurea users (adjusted between-group difference: 12.9 ng/mL; 95% CI 0.3 – 25.5; p=0.044). Although max CK was also higher among sulfonylurea users, the difference was not statistically significant compared to non-sulfonylurea users (mean [SD]: 1,901 [2,194] ng/mL versus 1,828 [2,325] ng/mL, respectively; adjusted between group difference: 96.8 ng/ml; 95% CI -401.7 – 595.3); p=0.703) (Table 5-2).

With respect to in-hospital composite events, more events occurred among sulfonylurea users (n=42, 28.8%) than non-sulfonylurea users (n=104,

25.1%), but this difference was not statistically significant (adjusted OR 1.05; 95% CI (0.63 – 1.73); p=0.86) (Table 5-3).

Glyburide vs. gliclazide

In the subgroup analysis of sulfonylurea users, 85 patients were using gliclazide and 60 were using glyburide prior to STEMI admission. The mean (SD) age for this group was 65.4 (12.4) years, 108 (74.5%) were men, 52 (35.9%) received primary percutaneous intervention, and 57 (39.3%) received fibrinolysis (Table 5-4). Baseline data were similar for both groups except that gliclazide users were more likely to have previous coronary reperfusion, hypercholesterolemia and use lipid lowering drugs.

Glyburide users had lower max cTnI compared to gliclazide users (mean [SD]: 45.3 [38.6] ng/mL versus 53.6 [91.5] ng/mL, respectively; p=0.533) (Table 5-2). After adjusting for baseline covariates and reperfusion management, the max cTnI was similar for both glyburide and gliclazide users (adjusted between-group difference: -6.9 ng/mL; 95% CI -37.0 – 23.6; p=0.662). Although max CK was higher among glyburide users, the difference was not statistically significant compared to non-sulfonylurea users (mean [SD]: 1,965.7 [2,163] ng/mL versus 1,879 [2,236] ng/mL, respectively; adjusted between group difference: -472.8 ng/mL; 95% CI -1,380.8 – 435.1); p=0.541) (Table 5-2).

There were more in-hospital composite events among glyburide users (n=22, 36.7%) compared to gliclazide users (n=20, 23.5%), but this difference was not statistically significant (adjusted OR 1.81; 95% CI (0.53 – 6.14); p=0.454) (Table 5-3).

5.5. Discussion

In this cohort of patients with STEMI and type 2 diabetes, sulfonylurea use was associated with larger infarct size compared to no sulfonylurea use. We found the maximum recorded troponin I levels within 48 hours of chest pain onset was 32% higher among sulfonylurea users compared to non-users. Sulfonylurea users also had higher total creatine kinase levels and more in-hospital cardiovascular events; though these comparisons did not reach

statistical significance. Additionally, we found no difference between gliclazide and glyburide with regard to infarct size.

Our findings are consistent with the detrimental effect of sulfonylureas on the heart observed in animal models. For example, Kristiansen and colleagues administered different sulfonylureas to excised diabetic rat hearts and observed larger infarct sizes and reduced left ventricular pressure and coronary blood flow with glyburide.[125] In other studies, animal hearts exposed to ischemic conditioning prior to the ischemia/reperfusion injury procedure, showed that sulfonylureas increase the size of infarction and contractile dysfunction.[129,130,244] Additionally, in animals treated with cardioprotective agents like nicorandil, sulfonylureas abolished the protective effects of these agents.[189] Other animal studies have shown an increased vascular resistance and decreased coronary blood flow as an effect of sulfonylureas.[126,127]

Our findings are consistent with and extend the observations from other studies of sulfonylurea use and myocardial infarct outcomes in humans. Klamann and colleagues used creatinine kinase increments to compare infarct size between 76 diabetes patients using sulfonylureas and 89 diabetes patients who did not use sulfonylureas.[145] Kottenberg and colleagues compared the troponin I area under the curve between 11 diabetes patients using sulfonylureas and 18 diabetes patients who were not using sulfonylureas.[245] Although both studies suggest larger infarct sizes associated with sulfonylurea use, the small sample sizes severely limited the ability to detect significant differences between groups.[145,245] In contrast to these two studies, Horsdal and colleagues found significantly higher troponin T and CK-MB levels in 307 patients using sulfonylureas compared to 736 patients not using sulfonylureas.[70] In the current study, we observed a significantly higher troponin I level in patients using sulfonylureas prior to admission. The total creatine kinase level was higher among sulfonylurea users; however, this did not reach statistical significance, likely due to the large variation in observed levels, low cardiac specificity of total creatine kinase and lack of statistical power to detect a difference.[256]

In the present study, we observed a trend towards more in-hospital composite events among sulfonylurea users; however, the difference was not statistically significant. Previous studies provide conflicting evidence with this

regard, as two studies with slightly larger sample sizes (487 and 1,310 patients) found a significantly higher risk of in-hospital events associated with sulfonylurea use;[69,123] while, two smaller studies (110 and 245 patients) found no association between sulfonylurea use and in-hospital event risk.[71,145] More evidence is warranted to investigate the association between sulfonylurea use and in-hospital event risk among type 2 diabetes patients with myocardial infarction.

Several in-vitro and animal studies have demonstrated larger myocardial infarct size in animals treated with glyburide compared to those treated with gliclazide.[125,189,257] Accordingly, we examined the effect of these drugs on infarct size in a group of type 2 diabetes patients. We found no difference in troponin I and total creatine kinase levels between gliclazide and glyburide users. As small sample size limited our ability to adequately compare between gliclazide and glyburide, further analysis with adequate power is warranted.

Two mechanisms have been proposed to explain the detrimental effects of sulfonylureas during myocardial infarction. First, sulfonylurea-induced hypoglycemia might trigger secretion of counter-regulatory hormones such as glucagon, epinephrine, norepinephrine, cortisol, and growth hormone. These hormones might increase heart rate and myocardial oxygen demand and decrease coronary blood supply by promoting coronary vasoconstriction, leading to myocardial ischemia and infarction.[258,259] However, we observed relatively high blood glucose levels (average 13 mmol/L) for both study groups, which might counter the hypoglycemia theory. Second, although sulfonylureas trigger insulin release by inhibiting ATP-sensitive potassium (K_{ATP}) channels on the pancreas, additional inhibition of cardiac K_{ATP} channels could be harmful.[138,170,260] Cardiac K_{ATP} channels are believed to play an important role in ischemic conditioning, a protective mechanism trigged by transient ischemia, such as pre-infarct angina, to limit infarct size at the time of acute ischemia.[106,260] By inhibiting cardiac K_{ATP} channels, sulfonylureas might block ischemic conditioning and increase infarct size.[119,189] It is worth noting that ischemic conditioning is an experimental concept in humans and the effect of aging, chronic drugs, and comorbidities on this protective mechanism is still unclear.[261]

Several study limitations should be considered when interpreting the results of this study. First, patients using sulfonylureas may be misclassified as

not having a STEMI because activation of cardiac K_{ATP} channels might play a role in ST elevation.[262] As sulfonylureas might inhibit cardiac K_{ATP} channels, they could theoretically mask any ST elevation. Indeed, Huizar and colleagues have demonstrated that diabetic patients using a sulfonylurea have a significantly reduced magnitude of ST elevation at the time of acute myocardial infarction as compared to those not using a sulfonylurea.[263] As our sampling frame was limited to the VHR registry, which included STEMI patients only, future studies should consider including patients with non-ST elevation myocardial infarction when examining the effect of sulfonylureas on infarct size. Second, the VHR registry did not record information on pre-infarct angina symptoms; hence, we were not able to control for pre-infarct angina. As this particular mechanism has been suggested to trigger ischemic conditioning,[264] it is important identify pre-infarction angina symptoms in future studies that examine the effect of sulfonylureas on myocardial infarct size. Third, as physicians could prescribe sulfonylureas to more frail patients, we cannot exclude the possibility of selection bias from this study. Fourth, we cannot be certain that the observed effect is related to sulfonylureas rather than a protective effect by other antidiabetic drugs. A more appropriately designed randomized placebo-controlled trial would be able to answer this question. Fifth, a more appropriate method to quantify infarct size would be the use of MRI or SPECT, which were not available in our patient group. However, maximum troponin levels correlate well with the aforementioned techniques.[248–251] Sixth, due to the small sample size, we could not evaluate the effect on infarct size among individual sulfonylureas. Animal model data would suggest there are important differences among these agents in regards to infarct size.[125,265]

Conclusions

In conclusion, we demonstrated that preadmission use of sulfonylureas is associated with larger infarct size compared to no sulfonylurea use in type 2 diabetes patients presenting with STEMI. Clinicians should consider the use of specific antidiabetic drug in the management of patients with type 2 diabetes, especially those at higher risk of myocardial infarction. However, our findings should be confirmed a randomized controlled trial.

Table 5-1. Baseline characteristics by sulfonylurea use

	No Sulfonylurea (n= 414)	*Sulfonylurea (n=146)*	*p-value*
Age, mean (SD), years	62.6 (12.8)	65.4 (12.4)	0.02
Males, n (%)	286 (69.1)	109 (74.7)	0.20
Body mass index, mean (SD), kg/m²	30.8 (7.2)	31.7 (10.8)	0.31
Cardiovascular risk factors, n (%)			
Hypertension	285 (68.8)	103 (70.1)	0.69
Hypercholesterolemia	247 (59.7)	83 (56.9)	0.62
Angina	120 (29.0)	51 (34.9)	0.41
Previous myocardial infarction	96 (23.2)	36 (24.7)	0.89
Previous coronary reperfusion	68 (16.4)	34 (23.3)	0.14
Ever smoked	284 (68.6)	100 (68.5)	0.46
Clinical data on admission, mean (SD)*			
Heart rate, beats/min	82.2 (24.5)	82.7 (22.3)	0.83
Systolic blood pressure, mm Hg	139.3 (31.5)	136.7 (28.8)	0.38
Diastolic blood pressure, mm Hg	82.7 (19.4)	83.1 (20.5)	0.82
Blood glucose, mmol/L	12.6 (8.4)	13.3 (5.4)	0.37
Serum creatinine, µmol/L	104.9 (74.7)	99.7 (45.6)	0.44
Total cholesterol, mmol/L	4.5 (1.4)	4.2 (1.3)	0.04
Reperfusion management			
Ischemia time (IQR), minutes	368 (147 – 2,880)	393 (163 – 1,880)	0.67
Reperfusion therapy, n (%)			0.69
Primary PCI	164 (39.6)	52 (35.6)	
Thrombolysis	154 (37.2)	57 (39.0)	
Preadmission antidiabetic drugs, n (%)			
Gliclazide	0	85 (58.2)	-
Glyburide	0	60 (41.1)	-
Glimepiride	0	1 (0.7)	-
Metformin	211 (51.0)	116 (79.5)	<0.01
Thiazolidinediones	18 (4.4)	22 (15.1)	<0.01
Sitagliptin	4 (1.0)	1 (0.7)	0.76
Insulin	107 (25.9)	19 (13.0)	<0.01
Other preadmission drugs, n (%)			
ACEI	114 (27.5)	60 (41.1)	<0.01
Angiotensin receptor blocker	58 (14.0)	19 (13.0)	0.73
Beta blocker	91 (22.0)	40 (27.4)	0.39
Calcium channel blocker	49 (11.8)	21 (14.4)	0.66
Antiplatelet	131 (31.6)	67 (45.9)	<0.01
Anticoagulant	13 (3.1)	7 (4.8)	0.58
Nitrate	40 (9.7)	12 (8.2)	0.65
Lipid lowering drug	163 (39.4)	59 (40.4)	0.97

* Earliest recorded measure after onset of chest pain or on admission
ACEI: angiotensin-converting-enzyme inhibitor, SD: standard deviation, PCI: percutaneous intervention, IQR: interquartile range

Table 5-2. Association between sulfonylurea use and maximum recorded cardiac enzymes within 48 hours of chest pain onset

	Troponin I	***Creatine Kinase***
Sulfonylurea vs. no sulfonylurea		
Mean levels (SD), ng/mL	49.8 (74.3) vs. 39.9 (50.4)	1,828.3 (2,325.4) vs. 1,901.8 (2,194.6)
Sulfonylurea use, between-group difference (95% CI)†	9.9 (-1.4 – 21.3)	73.5 (-389.5 – 536.5)
Adjusted model 1, between-group difference (95% CI)‡	12.9 (0.3 – 25.5)	96.8 (-401.7 – 595.3)
Adjusted model 2, between-group difference (95% CI)‡	27.4 (3.9 – 51.0)	621.7 (53.4 – 1190.0)
Glyburide vs. gliclazide		
Mean levels (SD), ng/mL	45.3 (38.6) vs. 53.6 (91.5)	1,965.7 (2,163.0) vs. 1,879.8 (2,236.0)
Sulfonylurea use, between-group difference (95% CI)†	-8.2 (-34.4 – 17.9)	85.9 (-702.2 – 873.9)
Adjusted model 1, between-group difference (95% CI)‡	-6.7 (-37.0 – 23.6)	-472.1 (-1,380.8 – 435.1)
Adjusted model 2, between-group difference (95% CI)‡	-11.9 (-63.5 – 39.7)	-499.4 (-1,630.8 – 632.1)

† Univariate model
‡ Model with adjustment for baseline demographics, cardiovascular risk factors, clinical data on admission, reperfusion management and concurrent drugs
SD: standard deviation, 95% CI: 95% confidence interval
Adjusted model 1: variables with missing values were imputed as described in methods
Adjusted model 2: only patients with complete data were included (no data imputation)

Table 5-3. Comparison of in-hospital composite events by sulfonylurea use

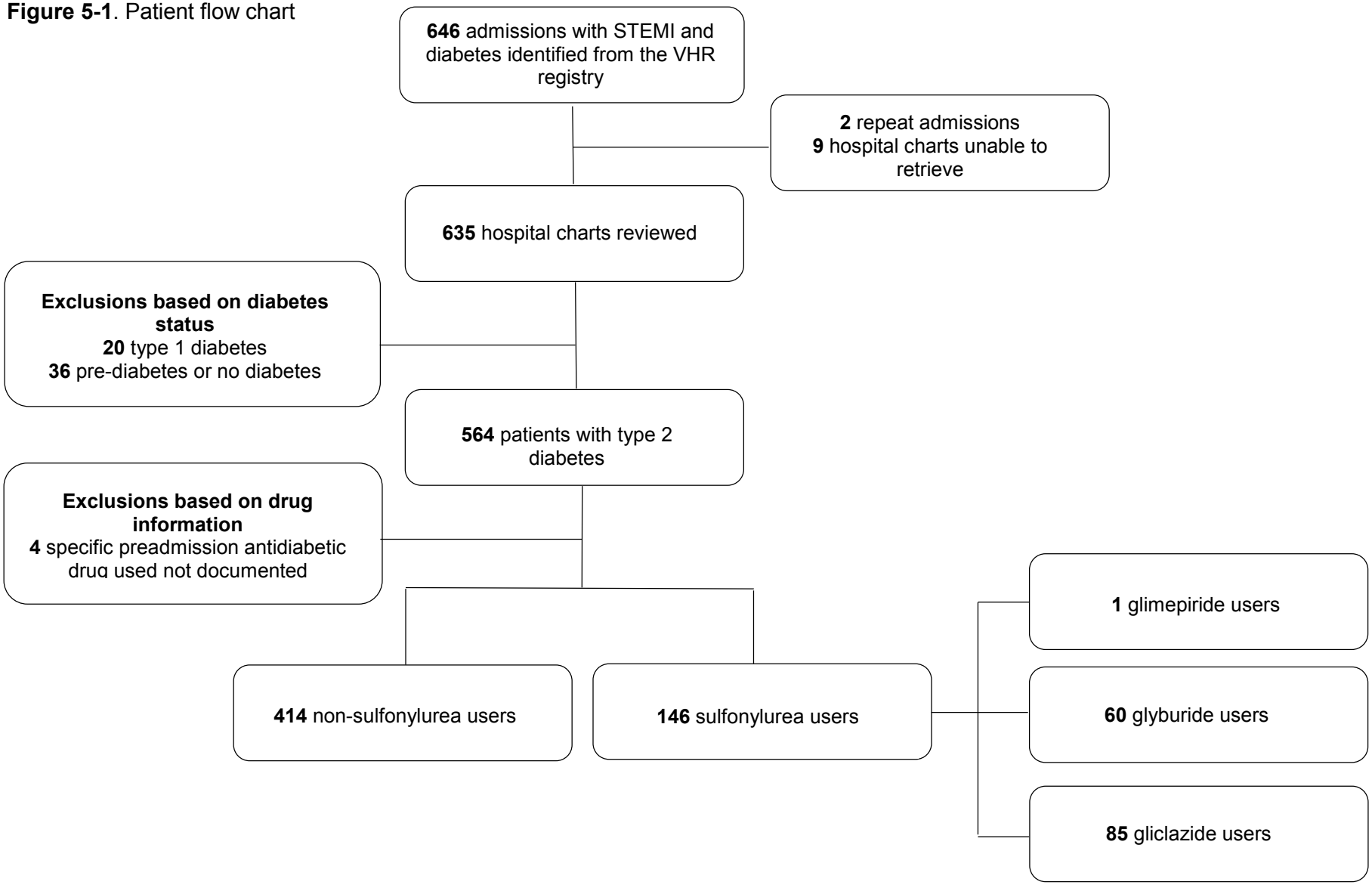
	No sulfonylurea (n=414)	*Sulfonylurea (n=146)*	*Gliclazide (n=85)*	*Glyburide (n=60)*
In-hospital cardiovascular events, n (%)	104 (25.1)	42 (28.8)	20 (23.5)	22 (36.7)
Heart failure	40 (9.7)	22 (15.1)	10 (11.8)	12 (20.0)
Cardiogenic shock	52 (12.6)	17 (11.6)	10 (11.8)	7 (11.7)
Cardiac arrest	48 (11.6)	16 (11.0)	8 (9.4)	8 (13.3)
Death	31 (7.5)	14 (9.6)	7 (8.2)	7 (11.7)

Table 5-4. Baseline characteristics by gliclazide and glyburide use

	Gliclazide (n= 85)	*Glyburide (n= 60)*	*p-value*
Age, mean (SD), years	64.8 (12.6)	66.2 (12.3)	0.51
Males, n (%)	60 (70.6)	48 (80.0)	0.20
Body mass index, mean (SD), kg/m²	32.4 (1.5)	30.6 (0.7)	0.35
Cardiovascular risk factors, n (%)			
Hypertension	59 (72.0)	43 (72.9)	0.90
Hypercholesterolemia	56 (68.3)	27 (51.0)	0.04
Angina	32 (42.1)	19 (32.8)	0.27
Previous myocardial infarction	22 (29.7)	14 (24.1)	0.48
Previous coronary reperfusion	26 (33.8)	8 (13.6)	0.01
Ever smoked	61 (82.4)	38 (71.7)	0.15
Clinical data on admission, mean (SD)*			
Heart rate, beats/min	80.9 (2.5)	85.3 (2.8)	0.25
Systolic blood pressure, mm Hg	139.3 (3.3)	132.6 (3.5)	0.19
Diastolic blood pressure, mm Hg	84.0 (2.3)	80.7 (2.3)	0.33
Blood glucose, mmol/L	13.1 (0.5)	13.7 (0.8)	0.48
Serum creatinine, µmol/L	98.6 (4.3)	101.4 (6.9)	0.72
Total cholesterol, mmol/L	4.1 (0.1)	4.2 (0.2)	0.74
Reperfusion management			
Ischemia time (IQR), minutes	490 (174 – 2,880)	299 (134 – 2,880)	0.26
Reperfusion therapy, n (%)			0.25
Primary PCI	33 (38.8)	19 (31.7)	
Thrombolysis	30 (35.3)	27 (45.0)	
Preadmission antidiabetic drugs, n (%)			
Metformin	66 (77.6)	50 (83.3)	0.40
Thiazolidinediones	12 (14.1)	10 (16.7)	0.67
Sitagliptin	1 (1.2)	0	-
Insulin	10 (11.8)	9 (15.0)	0.57
Other preadmission drugs, n (%)			
ACEI	38 (47.5)	21 (38.2)	0.28
Angiotensin receptor blocker	14 (17.5)	5 (9.1)	0.17
Beta blocker	28 (35.0)	12 (21.8)	0.10
Calcium channel blocker	13 (16.3)	7 (12.7)	0.57
Antiplatelet	43 (53.8)	24 (43.6)	0.25
Anticoagulant	5 (6.3)	2 (3.6)	0.50
Nitrate	8 (10.0)	4 (7.1)	0.56
Lipid lowering drug	42 (52.5)	17 (30.9)	0.01

* Earliest recorded measure after onset of chest pain or on admission
ACEI: angiotensin-converting-enzyme inhibitor, SD: standard deviation, PCI: percutaneous intervention, IQR: interquartile range

Figure 5-1. Patient flow chart



STEMI: ST-elevation myocardial infarction, VHR: vital heart response

CHAPTER 6

SUMMARY

6.1. Summary of Research

Adverse drug events are common and can lead to hospitalization or death.[1] Due to well-recognized limitations in premarketing clinical trials, many adverse events are not detected during the premarketing stages of a drug.[13] As millions of Canadians rely on drugs for every day management of disease, detecting and assessing drug safety signals is vital to public safety.[266,267] Although randomized controlled trials (RCTs) provide the highest level of evidence for causality, this study design may not be feasible nor ethical for answering a question of harm. An alternative approach to assess causal relationships for a drug safety signal using pharmacoepidemiology studies is to follow the Bradford-Hill considerations.[33]

Type 2 diabetes mellitus, and its cardiovascular complications, is reaching staggering epidemic levels around the world.[37] Oral antidiabetic drugs are a cornerstone in the management of type 2 diabetes; however, these drugs are not without possible adverse events. Indeed, recent cardiovascular safety concerns for some classes of antidiabetic drugs has prompted the Food and Drug Administration (FDA) to require evidence of cardiovascular safety for all new therapies.[48] Within this context, the safety of all antidiabetic drugs, including sulfonylureas, have come under careful scrutiny.

The cardiovascular safety of sulfonylureas has been the source of much debate for more than 40 years. The claim is based largely on the UGDP and several observational studies that might be subject to bias.[49,50] Findings from the UKPDS and other clinical trials; however, do not support the potential association between sulfonylureas and adverse cardiovascular events.[64,78] There is some evidence to support the Bradford-Hill considerations of biologic plausibility,

coherence, and analogy; however, the causal link between sulfonylureas and adverse cardiovascular events continues to be questioned. Possibly because the vast majority of previous studies did not recognize differences in pharmacological and pharmacokinetic properties among individual sulfonylureas with respect to risk of hypoglycemia, tissue selectivity, and the ability to abolish ischemic conditioning and block cardioprotective mechanisms at time of acute ischemia.[50] Promising upcoming large clinical trials could provide some clues towards the cardiovascular safety of sulfonylureas; though, results are not expected for several years.[84,85]

The overall objective of this program of research was to use the cardiovascular safety signal associated with sulfonylurea use as a case study to examine the application of Bradford-Hill considerations in the assessment of a causal relationship. Four separate, but interrelated, studies investigated several Bradford-Hill considerations that we believe were not adequately addressed in the current literature.

In the first study (Chapter 2), we examined the consideration of biologic plausibility by conducting a systematic review to pool observations from electrophysiological studies reporting the half-maximal inhibitory concentrations (IC_{50}) for sulfonylureas at pancreatic and cardiac receptors. These IC_{50} values were compared against the steady-state concentration for each sulfonylurea when given at usual therapeutic doses. We observed that individual sulfonylureas differ with respect to tissue selectivity characteristics at usual therapeutic doses. Given these observations, we categorized sulfonylureas into two main groups, sulfonylureas that are more likely to selectively bind to pancreatic receptors and sulfonylureas that non-selectively bind to both pancreatic and cardiac receptors. Accordingly, the latter group could theoretically abolish ischemic conditioning and interfere with cardioprotective mechanisms conferred by cardiovascular K_{ATP} channels activation at time of acute ischemia and; thus, leading to more adverse cardiovascular events.

To assess whether differences in tissue selectivity characteristics among sulfonylureas would translate into cardiovascular risk differences in clinical settings, we conducted two separate observational studies using provincial administrative healthcare databases (Alberta, Canada). The first (Chapter 3)

was a nested-case control study to investigate the strength of association between sulfonylureas and the risk of acute coronary syndrome. We found that patients using glyburide, a sulfonylurea that binds non-selectively to receptors in the pancreas and heart, had a small but significantly higher risk of acute coronary syndrome events than patients using gliclazide, a sulfonylurea that binds selectively to receptors in the pancreas.

To build on these findings, the objective of the second observational study (Chapter 4) was to determine if there is a dose-response relationship between sulfonylureas and a composite of major adverse cardiovascular events. We found that patients using higher doses of glyburide had a higher risk of major adverse cardiovascular events compared to patients using lower doses of the drug. In contrast, we did not observe a dose-related difference in cardiovascular risk for gliclazide users. Taken altogether, these findings add further evidence that the risk of adverse cardiovascular events varies among sulfonylureas, especially between glyburide and gliclazide.

In the last study (Chapter 5), we wanted to determine if there is coherence between observations that sulfonylureas affects infarct size in animal model studies and clinical events in humans. Evidence on this effect is scarce in humans and limited by small sample size. Therefore, we conducted a pilot study using data from a regional ST-elevation myocardial infarction (STEMI) registry to compare type 2 diabetes patients with and without sulfonylureas with respect to infarct size. By measuring maximum recorded troponin I levels within 48 hours of chest pain onset, we demonstrated that sulfonylurea users had a larger infarct size compared to non-sulfonylurea users. Unfortunately, the limited sample size in this pilot study did not give us the opportunity to examine the effect of individual sulfonylureas.

6.2. Significance of Research

Type 2 diabetes mellitus is a common, progressive chronic disease with increasing prevalence in Canada and around the world.[37,38] The burden of type 2 diabetes on the individual and our healthcare system is an important consideration, especially since the risk of cardiovascular events is significantly

higher in these individuals compared to the general population.[39] Although controlling hyperglycemia with antidiabetic drugs can reduce the risk of complications, these drugs appear to also have questions of cardiovascular safety.[64] Recent experiences with the thiazolidinediones (TZDs) have made clinicians and regulatory agencies more cautious and raised questions about the cardiovascular safety of new antidiabetic drugs.[268–270] Clinicians are also re-visiting the safety of sulfonylureas even though these drugs are familiar, have reliable efficacy to reduce glycaemia, and are available at low cost. Indeed sulfonylureas have been used for over 60 years to control hyperglycemia in people with type 2 diabetes.

The overall finding generated from this program of research identified important differences among sulfonylureas, with gliclazide appearing to be associated with a lower risk of adverse cardiovascular events compared to glyburide. Although this finding is based on a series of observational studies, it is unlikely that a randomized controlled trial will be conducted to directly compare the effects of these two drugs on cardiovascular outcomes. Therefore, considering that both drugs are readily available and have a similar cost, we recommend that clinicians consider prescribing gliclazide rather than glyburide for patients who require a sulfonylurea.

Although several individual studies reported the binding characteristics of sulfonylureas, we conducted a systematic review and summarized these findings across commonly used sulfonylureas. We added information on the steady state concentration of these sulfonylureas to further enhance our understanding of how the binding characteristics may vary among individual sulfonylureas. This work identified that some sulfonylureas selectively bind to pancreatic receptors while others bind to both cardiac and pancreatic receptors.

Understanding that there were differences in the pharmacokinetic and pharmacologic properties among sulfonylureas, we reviewed previous studies and found that few have examined the effect of individual sulfonylureas on the risk of cardiovascular disease.[120,198,204,271] Instead, most studies grouped sulfonylureas as one class to compare against a non-sulfonylurea reference group, such as metformin.[68,191,272–275] This approach might introduce selection bias in favor of patients using metformin who are usually younger, have less

severe hyperglycemia, have a shorter duration of diabetes, or have fewer comorbidities compared to patients using a sulfonylurea.[56] Inadequate control for these differences in observational studies would lead to a perceived increased risk of adverse cardiovascular events associated with sulfonylurea use.[276] Given our observations from the systematic review, we believe sulfonylureas should be considered individually when examining cardiovascular safety.

Evidence of a dose-response relationship between sulfonylureas and adverse cardiovascular events is limited.[135,136] Our study built on previous studies by examining a different patient population, an additional sulfonylurea (gliclazide), and different outcome measures. In addition, our study used an exposure definition that allowed for changes over time. Previous studies used the cumulative exposure over the entire observation period, which might not accurately define exposure because the dose may change over time to accommodate changes in glucose control or reduce the risk of hypoglycemia.[135,136]

Last, our findings are consistent with the detrimental effect of sulfonylureas myocardial infarction size observed in animal models.[125,244] There is, however, limited evidence of sulfonylurea effects on myocardial infarction size in humans. Previous studies found larger infarct sizes with sulfonylureas; however, the small sample sizes severely limited the ability to detect significant differences between groups.[70,145,245] Using a regional STEMI registry, we observed larger infarct size among patients using sulfonylureas compared to patients not using sulfonylureas.

Collectively, this line of research provides evidence that there are important differences in the risk of adverse cardiovascular events among sulfonylureas. For over forty years, inconsistences between findings from clinical trials and observation studies on the cardiovascular safety of sulfonylureas have cautioned against the use of these drugs. As current RCTs on this topic are not expected for years, reliance on pharmacoepidemiology methods to assess the cardiovascular safety of sulfonylureas is warranted. We approached this by evaluating elements of the Bradford-Hill considerations for casual relationships. We provided a case study on using these elements to assess causality in pharmacoepidemiology studies. If anything, the conclusions herein are

hypothesis generating and will stimulate more research in the area of sulfonylurea and cardiovascular disease.

6.3. Implications for Future Research

A. Consider Potential Confounders

While our research built on and extended the existing evidence to support a causal link between sulfonylurea use and adverse cardiovascular events, additional research would solidify this relationship. A key limitation of our research is the reliance on data from administrative sources, which lack information on well-known cardiovascular risk factors, such as smoking status, diet, physical activity, HbA1c, BMI, blood pressure and cholesterol level. However, our results are consistent with other studies that have included information on such confounders.[65,271] Future studies, nevertheless, should consider such variables as a means to confirm and strengthen our findings.

B. Consider the Safety of Individual Sulfonylureas

As we demonstrated in our program of research, the risk of adverse cardiovascular events appears to differ among individual sulfonylureas. Although all sulfonylureas have the same insulinotropic mechanism of action, individual drugs differ in pharmacokinetic properties, risk of hypoglycemia, tissue selectivity characteristics, and ability to abolish ischemic conditioning and block cardioprotective mechanisms at time of acute ischemia. Hence, future studies examining the cardiovascular safety of sulfonylureas should not group them in one class; but rather, examine the effect of individual sulfonylureas on the risk of adverse cardiovascular events.

We mainly focused in our studies on two sulfonylureas, gliclazide and glyburide. Other sulfonylureas were not included either because of limited sample size (tolbutamide) or were not widely used in our health jurisdiction (glipizide and glimepiride). As differences between these drugs have been noted, future studies should investigate the cardiovascular safety of other sulfonylureas that were not included in our studies, such as glimepiride.

C. Consider a Randomized Controlled Trial

Although it is unlikely to be conducted, a RCT would provide conclusive evidence to support or refute the causal link between sulfonylureas and adverse cardiovascular effects. If a future RCT is ever considered, we would recommend that the following two questions be addressed.[50]

- First, "*do sulfonylureas, as a group, increase the risk of adverse cardiovascular events in people with type 2 diabetes?"* Both the TOSCA.IT and the CAROLINA trials will help to provide some answers to this question.[84,85] However, glimepiride, the sulfonylurea used in the CAROLINA trial, is not commonly used in Canada and other health jurisdictions, therefore the trial results may not be widely generalizable. More importantly, both TOSCA.IT and CAROLINA are investigating the *relative* safety of sulfonylureas by comparing the risk of cardiovascular events with other antidiabetic drugs. To truly examine cardiovascular safety of these drugs, we would recommend comparing sulfonylurea use to a placebo, as recent cardiovascular outcome trials like the TECOS and ELIXA trials have done.[277,278]

- Second, "*is the risk of adverse cardiovascular events different among individual sulfonylureas in people with type 2 diabetes?"* Although the TOSCA.IT is including multiple sulfonylureas, patients are not randomly assigned to individual agents and the CAROLINA study is only using glimepiride.[84,85] To help address this issue, we recommend using sulfonylureas with different pharmacokinetic and pharmacologic properties, such as glimepiride, gliclazide, and glyburide.[205]

D. Consider the Underlying Biologic Mechanisms

Another area of research is to differentiate between the underlying biological mechanisms explaining the potential harmful cardiovascular effects of sulfonylureas. Future studies should be designed to improve our understanding of how the possible biologic mechanisms (including hypoglycemia, abolition of K_{ATP}-mediated cardioprotective mechanisms, accumulation of visceral fat, and changes to the proinsulin:insulin ratio) can explain the cardiovascular risk of sulfonylureas. In addition, future studies should consider how differences in

pharmacokinetic properties and tissue selectivity characteristics affect these mechanisms.

Hypoglycemia

Sulfonylurea-induced hypoglycemia might precipitate a cardiac stress leading to myocardial ischemia and QT prolongation.[109] This mechanism is largely based on evidence from clinical studies suggesting harmful cardiac effects with acute hypoglycemia in patients with type 2 diabetes.[101,103] Surprisingly, we noted in our myocardial infarct size study (chapter 5) high admission blood glucose levels among sulfonylurea users. Therefore, the role of sulfonylurea-induced hypoglycemia in adverse cardiovascular events requires further investigation. Moreover, since sulfonylureas vary in terms of time to maximum blood concentration, half-life, metabolism, and elimination, the influence of these pharmacokinetic properties on the risk of hypoglycemia should be considered.[52,111] For example, since glyburide is affected more by reductions in renal function (50% excreted unchanged in urine) compared to gliclazide (<1% excreted unchanged in urine)[112,113,115] indicators of renal function like serum creatinine or estimated creatinine clearance should be considered in future studies.

K_{ATP}-mediated cardioprotective mechanisms

As we noted in our systematic review of ***sulfonylurea binding affinities*** (chapter 2), many of the included experiments examined animal tissues and cloned K_{ATP} channels expressed in different cell lines under a variety of experimental conditions. We recommend that any future study should conduct such experiments in unified experimental conditions using human tissue samples. This approach would provide more direct comparisons of the binding affinities among sulfonylureas.

Although it has been replicated in many animal models, ***ischemic conditioning*** is still an experimental concept in humans.[279–281] The clinical usefulness of different variations of ischemic conditioning, i.e. remote pre-conditioning and post-conditioning, are subject of ongoing research.[282–286] It is likely, however, that pre-infarct angina and vigorous exercise play a role in triggering ischemic conditioning in humans.[287,288] Nevertheless, laboratory

evidence suggest in the absence of such triggers, activation of cardiac K_{ATP} channels might still be cardioprotective regardless to ischemic conditioning.[260] Protection of cardiac myocyte in this case may result from reduced cardiac contractility and oxygen demand and increased coronary blood flow.[60,260] Interestingly, Kristiansen et al demonstrated, in the absence of ischemic conditioning, that glyburide-treated diabetic rats had larger infarct size and reduced coronary flow than gliclazide-treated diabetic rats.[125] It is still unclear, however, the role of these mechanisms in humans and the interaction with advanced age, long-standing diabetes and chronic use of sulfonylureas. It is also noteworthy that pharmacokinetic properties of sulfonylureas might affect its propensity to inhibit cardiovascular K_{ATP} channels; hence, sulfonylureas with long duration of action, affected more by renal impairment, or have active metabolites could have a higher chance of retaining drug at the site of action to block cardiovascular K_{ATP} channels.[52,111,121]

We did not observe a significant difference between gliclazide and glyburide with respect to ***myocardial infarction size*** in type 2 diabetes patients presenting with STEMI (chapter 5), probably due to low power. However, a future study with enough sample size should be able to answer this question. Additionally, this future study should include non-STEMI patients, as sulfonylureas might mask ST elevation, and capture pre-infarct angina symptoms in order to appropriately examine the effect of sulfonylureas on infarct size.[263]

Finally, the ***antiarrhythmic properties*** of sulfonylureas, which have been observed in some animal models but not fully explored in humans, warrants further investigation.[108]

E. Consider Exposure Definitions

A final consideration for future studies comes from our dose-response study (chapter 4). In this study, we introduced a new model to assess time-dependent dose level to characterize exposure to a drug during follow up in an observational study. Previous studies have assessed dose level either at baseline or used the entire observation period to capture cumulative exposure.[135,289] As the accurate characterization of exposure is critical for

examining associations[121,290], further work is needed to find the most appropriate method.

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APPENDICES

Appendix A. Observational studies assessing the cardiovascular safety of sulfonylureas

Year	*Study*	*Country*	*Treatment arms*	*Observation period*	*Type*	*Sample size*	*Duration of follow-up*
2015	Fadini[1]	Italy	Sulfonylurea, TZD, DDP-4i	2010-2013	Cohort	127,555	2.6 years
	Kannan[2]	US	Sulfonylurea, TZD, DDP-4i, GLP-1a	2005-2013	Cohort	13,185	4 years
	Yu[3]	UK	Sulfonylurea, DDP-4i	2007-2012	Cohort	11,807	≈ 1 year
	Seong[4]	Korea	Sulfonylurea, Pioglitazone, DDP-4i	2006-2010	Cohort	349,476	≈ 0.6 years
	Mogensen[5]	Denmark	Gliclazide, Glimepiride, Glipizide, Glyburide, Tolbutamide, Repaglinide	1997-2009	Cohort	56,827	4.1 years
	Mogensen[6]	Denmark	Gliclazide, Glimepiride, Glipizide, Glyburide, Tolbutamide, Metformin	1997-2009	Cohort	25,404	3.1 years
	Huang[7]	Canada	Gliclazide, Glyburide, Repaglinide	1998-2010	Cohort	6,283	≈ 30 days
2014	Roumie[8]	US	Sulfonylurea, Insulin	2001-2011	Cohort	42,938	14 months
	Li[9]	US	Sulfonylurea, No Sulfonylurea	2000-2010	Cohort	4,902	6.9 years
	Mogensen[10]	Denmark	Sulfonylurea, DDP-4i, GLP-1a, Insulin	2007-2011	Cohort	40,028	2.1 years
	Girman[11]	US	Sulfonylurea, Metformin	2003-2010	Cohort	226,267	NR
	Morgan[12]	UK	Sulfonylurea, DDP-4i	2000-2010	Cohort	41,847	1.9 years
2013	Currie[13]	UK	Sulfonylurea, Metformin, Insulin	2000-2010	Cohort	84,622	2.8 years
	Abdelmoneim[14]	Canada	Gliclazide, Glyburide	1998-2010	Case-Control	4,239 Cases 16,723 Controls	5.5 years
	Nagendran[15]	Canada	Sulfonylurea, No Sulfonylureas	2002-2006	Cohort	21,023	30 days

Year	Study	Country	Treatment arms	Observation period	Type	Sample size	Duration of follow-up
	Hung[16]	Taiwan	Glimepiride or Glyburide, Metformin	1998-2007	Cohort	1,159	3.1-3.8 years
	Bo[17]	Italy	Gliclazide, Glyburide, Tolbutamide	1996-2011	Cohort	1,277	14 years
2012	Juurlink[18]	Canada	Gliclazide, Glyburide	2007-2010	Cohort	2,674	0.6-0.9 years
	Pantalone[19]	US	Glimepiride, Glipizide, Glyburide, Metformin	1998-2006	Cohort	23,915	2.2 years
	Pantalone[20]	US	Glimepiride, Glipizide, Glyburide, Metformin	1998-2006	Cohort	7,320	2.4 years
	Roumie[21]	US	Sulfonylurea, Metformin	2001-2008	Cohort	253,690	0.6-0.8 years
2011	Jørgensen[22]	Denmark	Gliclazide, Glimepiride, Glipizide, Glyburide, Tolbutamide	1997-2006	Cohort	400	1 year
	Schramm[23]	Denmark	Gliclazide, Glimepiride, Glipizide, Glyburide, Tolbutamide, Metformin	1997-2006	Cohort	120,020	2-2.2 years
	Sullivan[24]	International	Sulfonylurea, Metformin, Diet only	1998-2000	Cohort	6,005	5 years
	Anderson[25]	Denmark	Gliclazide, Glimepiride, Glipizide, Glyburide, Tolbutamide	1997-2006	Cohort	3,477	744 days
	Mellbin[26]	Sweden	Sulfonylurea, Non-sulfonylurea	1998-2005	Cohort	1,145	4.1 years
	Horsdal[27]	Denmark	Sulfonylurea, Metformin, Insulin	1996-2004	Case-Control	10,616 Cases 90,697 Controls	≈ 90 days
	Horsdal[28]	Denmark	Sulfonylurea, Metformin, Insulin	2003-2006	Cohort	4,817	≈ 1 year
2010	Sillars[29]	Australia	Sulfonylurea, Metformin	1993-2007	Cohort	1,271	10.4 years
	Azoulay[30]	UK	Sulfonylurea, Metformin	1988-2008	Case-Control	14,996 Cases 145,366 Controls	4.3 years
	Roussel[31]	International	Sulfonylurea, Metformin	2003-2006	Cohort	8,400	20.9 months
	Jorgnsen[32]	Denmark	Gliclazide, Glimepiride, Glipizide, Glyburide, Tolbutamide, Metformin	1997-2006	Cohort	9,876	2.2 years

Year	Study	Country	Treatment arms	Observation period	Type	Sample size	Duration of follow-up
	Pantalone[33]	US	Glimepiride, Glipizide, Glyburide	1998-2006	Cohort	11,141	2.4 years
	Zeller[34]	France	Gliclazide, Glimepiride, Glyburide, Non-sulfonylurea, Insulin, Diet	2005	Cohort	1,310	NR
	Andersson[35]	Denmark	Sulfonylurea, Metformin	1997-2006	Cohort	10,920	2.3 years
	Hsiao[36]	Taiwan	Sulfonylurea, TZD	2000-2005	Cohort	8,138	2.2 years
	MacDonald[37]	UK	Sulfonylurea, Metformin, TZD, Insulin, Diet	1988-2007	Case-Control	1,633 Cases 1,633 Controls	NR
	Brownstein[38]	US	Sulfonylurea, Rosiglitazone	2000-2006	Cohort	34,253	2.3 years
2009	Khalangot[39]	Ukraine	Gliclazide, Glimepiride, Glyburide	1998-2007	Cohort	64,288	1.5 years
	Horsdal[40]	Denmark	Gliclazide, Glimepiride, Glipizide, Glyburide, Tolbutamide	1996-2004	Cohort	3,448	1 year
	Pantalone[41]	US	Sulfonylurea, Metformin, Pioglitazone, Rosiglitazone	1998-2006	Cohort	20,450	6 years
	Hsiao[42]	Taiwan	Sulfonylurea, Pioglitazone, Rosiglitazone	2001-2005	Cohort	473,483	1.6-3.1 years
	Tzoulaki[43]	UK	First Generation Sulfonylureas, Second Generation Sulfonylureas, Metformin	1990-2005	Cohort	91,521	7.1 years
	Dormuth[44]	Canada	Sulfonylurea, Pioglitazone, Rosiglitazone	1997-2007	Case-Control	2,244 Cases 8,903 Controls	2 years
	Arruda-Olson[45]	US	Sulfonylurea, Insulin, Diet only	1985-2002	Cohort	386	4.9 years
2008	Mellbin[46]	Sweden	Sulfonylurea, Non-sulfonylurea	1998-2003	Cohort	1,181	12 months
	Horsdal[47]	Denmark	Sulfonylurea, Metformin, Insulin	1996-2004	Cohort	8,494	1 year
	Mcalister[48]	Canada	Sulfonylurea, Metformin	1991-1999	Cohort	5,631	4.7 years

Year	Study	Country	Treatment arms	Observation period	Type	Sample size	Duration of follow-up
	Evans[49]	Scotland	Pancreatic-specific: (Chlorpropamide, Gliclazide, Glipizide, Tolbutamide) Nonspecific (Glimepiride, Glyburide)	1994-2001	Cohort	3,331	2.9 years
	Gosmanova[50]	US	Sulfonylurea, Metformin	2000-2006	Cohort	2,206	62 months
	Wells[51]	US	Sulfonylurea, Meglitinide, Biguanide, TZD	1998-2006	Cohort	33,067	28.6 months
	Sadikot[52]	India	Gliclazide, Glipizide, Glimepiride, Glyburide	2004-2005	Case-Control	76 Cases 152 Controls	NR
	Walker[53]	US	Sulfonylurea, Rosiglitazone, Pioglitazone	2000-2007	Cohort	351,518	7.1 years
2007	Monami [54]	Italy	Gliclazide, Glyburide	1998-2001	Cohort	568	4.4 – 5 years
	Kahler[55]	US	Sulfonylurea, Metformin, TZD, No drug	1998-2000	Cohort	39,721	≈ 15 months
	Lipscombe[56]	Canada	Sulfonylurea, Meglitinide, Metformin, Pioglitazone, Rosiglitazone, Acarbose, Insulin	1998-2005	Case-Control	30,265 Cases 150,650 Controls	3.8 years
	Johannes[57]	US	Sulfonylurea, Metformin, TZD	1999-2002	Cohort	25,140	≈ 15 months
	Mcafee[58]	US	Sulfonylurea, Metformin, Rosiglitazone	2000-2004	Cohort	31,017	1.1 years
2006	Monami[59]	Italy	Gliclazide, Glimepiride, Glyburide, Repaglinide	1993-2004	Cohort	587	2.6 years
	Evans[60]	Scotland	Sulfonylurea, Metformin, Sulfonylurea and Metformin	1994-2001	Cohort	5,730	8 years
	Simpson[61]	Canada	Glyburide, First Generation Sulfonylurea	1991-1999	Cohort	4,258	4.6 years
	Sauer[62]	US	Sulfonylurea, Metformin, TZD	1998-2002	Case-Control	203 Cases 308 Controls	4.6 years

Year	Study	Country	Treatment arms	Observation period	Type	Sample size	Duration of follow-up
	Johnsen[63]	Denmark	Gliclazide, Glimepiride, Glipizide, Glyburide, Tolbutamide, people with no diabetes	1994-2002	Case-Control, Cohort	6,738 Cases 67,374 Controls	90 days
2005	Johnson[64]	Canada	Sulfonylurea, Metformin	1991-1999	Cohort	5,720	5 years
	Danchin[65]	France	Sulfonylurea, No sulfonylurea	2000	Cohort	487	NR
	Eurich[66]	Canada	Sulfonylurea, Metformin	1991-1996	Cohort	1,833	2.5 years
2004	Mannucci[67]	Italy	Sulfonylurea, Metformin	1993-2003		374	4.6 years
	Gulliford[68]	UK	Sulfonylurea, Metformin	1992-1998	Cohort	8,488	2.1-2.2 years
	McGuire[69]	International	Insulin providing (Sulfonylurea and Insulin), Insulin-sensitizing (Biguanide and TZD)	1997-1999	Cohort	1,573	1 year
2002	Johnson[70]	Canada	Sulfonylurea, Metformin	1991-1999	Cohort	8,866	5.1 years
2001	Halkin[71]	Israel	Sulfonylurea, Oral Non-sulfonylurea, Insulin, Diet	NR	Cohort	245	1 year
	Fisman[72]	International	Glyburide, Metformin, Diet only	NR	Cohort	11,322	4 years

DDP-4i, Dipeptidyl peptidase-4 inhibitors; GLP-1a: Glucagon-like peptide-1 agonists; NR: not reported; TZD: Thiazolidinedione; UK: United Kingdom; US: United States

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Appendix B. Systematic review search strategy

Element of Interest	*Search Terms*
Sulfonylurea compounds	1. exp sulfonylurea derivative/
	2. (tolbutamide or gliclazide or glibenclamide or mitiglinide or meglitinide or nateglinide or glimepride or repaglinide or carbutamide or chloropropramide or glibornuride or glipizide or gliquidone or glisentide).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
	3. 1 or 2
Potassium channel	4. exp potassium channel/
	5. kir6*.ti,ab.
	6. (((k adj atp) or katp or K+) adj channel*).ti,ab.
	7. "inwardly rectifying potassium channel subunit Kir6.2"/
	8. (SUR1* or SUR2*).ti,ab.
	9. or/4-8
Tissue selectivity	10. exp binding affinity/
	11. stoichiometry/
	12. tissue specificity/
	13. (affinity or binding or selectiv* or sensitiv*).ti,ab.
	14. or/10-13
	15. exp pancreas islet beta cell/
	16. heart muscle/ or heart muscle cell/
	17. exp smooth muscle/
	18. exp vascular smooth muscle/
	19. cell receptor/ and animal cell/
	20. or/15-19
Combine the three elements	21. 3 and 9 and 14 and 20

Appendix C. Ethics approval of included studies

Health Research Ethics Board

308 Campus Tower
University of Alberta, Edmonton, AB T6G 1K8
p. 780.492.9724 (Biomedical Panel)
p. 780.492.0302 (Health Panel)
p. 780.492.0459
p. 780.492.0839
f. 780.492.7808

APPROVAL FORM

Date: October 9, 2009

Principal Investigator:	Scot Simpson
Study ID:	Pro00009813
Study Title:	Is there a difference in cardiovascular risk amongst the sulfonylureas?
Approval Expiry Date:	October 8, 2010
Sponsor/Funding Agency:	Canadian Diabetes Association CDA

Thank you for submitting the above study to the Health Research Ethics Board (Health Panel). Your application has been reviewed and approved on behalf of the Research Ethics Board.

This is research using data which are de-identified by Alberta Health & Wellness prior to release to research team.

A renewal report must be submitted next year prior to the expiry of this approval if your study still requires ethics approval. If you do not renew on or before the renewal expiry date, you will have to re-submit an ethics application.

Approval by the Health Research Ethics Board does not encompass authorization to access the patients, staff or resources of Capital Health or other local health care institutions for the purposes of the research. Enquiries regarding Capital Health administrative approval, and operational approval for areas impacted by the research, should be directed to the Capital Health Regional Research Administration office, #1800 College Plaza, phone (780) 407-1372.

Sincerely,

Glenn Griener, Ph.D.
Chair, Health Research Ethics Board (Health Panel)

Note: This correspondence includes an electronic signature (validation and approval via an online system).

Approval

Date:	May10, 2013
Study ID:	Pro00037529
Principal Investigator:	Scot Simpson
Study Title:	Comparison of infarct size between type 2 diabetic patients using gliclazide or glyburide
Approval Expiry Date:	May 9, 2014

Thank you for submitting the above study to the Health Research Ethics Board - Health Panel . Your application has been reviewed and approved on behalf of the committee.

The Health Research Ethics Board assessed all matters required by section 50(1)(a) of the Health Information Act. It has been determined that the research described in the ethics application is a retrospective chart review for which subject consent for access to personally identifiable health information would not be reasonable, feasible or practical. Subject consent therefore is not required for access to personally identifiable health information described in the ethics application.

In order to comply with the Health Information Act, a copy of the approval form is being sent to the Office of the Information and Privacy Commissioner.

A renewal report must be submitted next year prior to the expiry of this approval if your study still requires ethics approval. If you do not renew on or before the renewal expiry date (May 9, 2014), you will have to re-submit an ethics application.

Approval by the Health Research Ethics Board does not encompass authorization to access the patients, staff or resources of Alberta Health Services or other local health care institutions for the purposes of the research. Enquiries regarding Alberta Health approvals should be directed to (780) 407-604. Enquiries regarding Covenant Health approvals should be directed to (780) 735-2274.

Sincerely,

Dr. Jana Rieger
Chair, Health Research Ethics Board - Health Panel

Note: This correspondence includes an electronic signature (validation and approval via an online system).

Appendix D. International Classification of Diseases (ICD) codes

Disease	*ICD-9*	*ICD-10*	*Procedural codes*
Cardiovascular mortality	39x – 45x	Ixx	-
Acute coronary syndrome	410, 411	I20.0, I21, I24.0, 124.8, I24.9	36.01, 36.02, 36.05 1.IJ.50^^, 1.IJ.57.GQ^^, 1.IJ.54.GQ-AZ
Stroke	362.3, 430, 431, 433.x1, 434.x1, 436, 435	H34.1, I60-I64, G45	-
Ischemic heart disease	410 – 414	I20-I25	-
Cerebrovascular disease	362.24, 430-438	I60-I69, G45, G46	-
Hyperlipidemia	272.0-4	E78.0-5	-
Hypoglycemia	250.8, 251.0, 251.1, 251.2, 962.3	E16.0, E16.1, E16.2, T38.3	-
Neuropathy	354.x, 355.x, 250.6, 337.1, 249.6, 357.2, 358.1, 536.3, 713.5, 456.2	E10.4, E11.4, E12.4, E13.4, E14.4, G73.0, G99.0, G59.0, G63.2	-
Retinopathy	249.5, 362.0, 250.5, 362.0, 362.81 ,362.82, 362.83, 362.442, 365.44, 366.44, 365.44, 366.41, 362.14, 362.16, 369.x	H36.0, H28.0, E10.3, E11.3, E12.3, E13.3, E14.3,	-
Nephropathy	250.4, 581.1, 581.8, 583.8, 582.1, 593.9, 584.5, 584.6, 584.7, 584.8, 586.0, 587.0, 796.0	N08.3, E10.2, E11.2, E12.2, E13.2, E14.2	-